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A SYNDROME CHARACTERIZED BY PRIMARY OVARIAN INSUFFICIENCY AND DECREASED STATURE

REPORT OF 11 CASES WITH A DIGRESSION ON HORMONAL CONTROL OF AXILLARY AND PUBIC HAIR*†

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WHEN one encounters lack of sexual development together with decrease in stature, a generalized deficiency of all elements of the anterior pituitary (panhypopituitarism) naturally comes to mind as the probable primary disturbance. It is the purpose of this paper to call attention to another syndrome which has these two features but in which the sexual infantilism at least is due to primary ovarian-lack rather than to primary pituitary disease. As will appear below, this syndrome has not gone entirely without notice in the literature.

The features which characterize this syndrome are the following:

1. The patients are short in stature but not actually dwarfs as is usually the case in panhypopituitarism.

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2. They have infantile mammæ, uteri, and vaginæ; in this respect they resemble the pituitary dwarfs.

3. In spite of complete absence of breast and uterine development, they usually have a small amount of axillary and pubic hair in contrast to the pituitary dwarfs who do not have any hair in these regions.

4. They are rather strong and well nourished, in contrast to the pituitary dwarfs who tire easily and who have difficulty in putting on weight.

5. The bone age is usually a few years retarded but in most cases the epiphyses eventually unite; in the pituitary dwarf, on the other hand, the bone age is much more retarded and the epiphyses often never unite. As in other conditions with retarded bone age—hypothyroidism and panhypopituitarism—"epiphysitis" is common.

6. There is constantly present in the urine an increase above normal of follicle-stimulating-hormone (FSH); in pituitary dwarfs, of course, this hormone is absent.

7. The "17-ketosteroid excretion" in the urine[15] (circa 2 to 5 mg. per 24 hours), though lower than that in normal females (circa 6 to 18 mg. per 24 hours), is considerably higher than that in pituitary dwarfs (circa 0 to 1.5 mg. per 24 hours).

8. Estrin therapy leads to the development of normal amounts of axillary and pubic hair; estrin therapy in pituitary dwarfism has no such effect.

9. The insulin tolerance test (ITT) shows normal hypoglycemia responsiveness as opposed to hypoglycemia unresponsiveness in pituitary dwarfism.[14]

10. Congenital anomalies in addition to the congenital absence or malformation of the ovaries are common; coarctation of the aorta and webbing of the neck are especially frequent.

11. Diffuse osteoporosis reminiscent of that seen in postmenopausal osteoporosis is common; precocious senility occurs as in panhypopituitarism.

Case Histories. CASE 1. D. W. S., No. 91914, entered this hospital in 1933 at the age of 21. She had developed axillary and pubic hair at the age of 19 but her breasts had never developed and she had never had a real menstrual period, although on several occasions she had had a slight bloody discharge from the vagina. She had been born 1 month prematurely and retarded growth had first been noted at 10; she had "stopped growing" at the age of 15.

On physical examination she was 4 feet 8½ inches; her span was 2.4 cm. greater than her height. Nutrition was excellent (see Fig. 1). There was no breast development and only a small amount of pubic hair and almost no axillary hair. The breast development and abundant pubic hair shown in Figure 1 were the result of 6 months of estrin therapy at the age of 28. Her genitalia were infantile and no uterine tissue could be felt by rectum. Blood pressure was 138/95.

When first Roentgen rayed at the age of 21, her bone age was more than 2 and less than 6 years retarded; at the age of 28 all epiphyses were closed.

The basal metabolic rate determinations were +14 and +3 respectively. An FSH test for 40 mouse units per 100 cc. of urine was positive; two 17-ketosteroid urinary assays were 4.7 and 3.9 mg. per 24 hours respectively.

While in the hospital under observation, the patient had undulant fever and the agglutination test for *Brucella melitensis* was positive. This suggested the possibility that the cause for the ovarian deficiency was a chronic infection of the ovaries with one of the brucella group of organisms. However, the patient made a spontaneous recovery from the fever and the diagnosis was never confirmed.

CASE 2. R. F., No. 133054, was first seen in 1938 at the age of 15. She was then 4 feet 6 inches tall and thought she had grown 1½ inches during the preceding year. She had never had a menstrual period. Her parents and 2 brothers were of normal height. The patient had been born at full term weighing 6 pounds but had always been undersized in spite of the fact that her general health had always been excellent.

She was sturdy in appearance (see Fig. 1), weighed 81 pounds, but was sexually undeveloped; there was no breast tissue and very little axillary and pubic hair; the external genitalia were infantile. Her span was 7.7 cm. greater than her height. Blood pressure was 104/70.

Roentgen ray films of her bones taken 2 years later at the age of 17 showed that her bone age was more than 4 and less than 6 years retarded. An FSH test for 10 mouse units per 100 cc. of urine was positive; two 17-ketosteroid assays were 3.9 and 3.6 mg. per 24 hours respectively.

CASE 3. C. M., No. 51984, was first seen in 1939 at the age of 22. She had never had a menstrual period and had had hot flashes since the age of 14. Rate of growth had decreased at the age of 8. Other members of her family were short but she was very much the shortest. She had been born 2 months prematurely and had had mumps at the age of 4.

On physical examination she was 4 feet 6 inches with a span 1.5 cm. greater than her height; she was fairly well nourished and weighed 88½ pounds. Her breasts were not developed and there was no axillary or pubic hair; the genitalia were infantile. Blood pressure was 120/70.

Her bone age was more than 7 and less than 8 years retarded; Roentgen rays taken 2 years later showed retardation of more than 5 and less than 9 years. In addition the Roentgen rays showed "epiphysitis" of several vertebræ (*cf.* Cases 4, 9, 10 and 11). The serum calcium was 10 mg. per 100 cc.; serum phosphorus, 3.9 mg. per 100 cc.; and the serum phosphatase, 6.4 Bodansky units. The insulin tolerance test showed normal findings. The basal metabolic rate was −6%. Two 17-ketosteroid assays were 4.7 and 4.7 mg. per 24 hours respectively. The FSH tests for 10 and 20 mouse units per 100 cc. were positive.

Peritoneoscopic examination showed an infantile uterus in normal position; the right tube was visualized as far as the fimbriated end; there was no evidence of any right ovary; no ovarian tissue could be seen on the left side either.

CASE 4. U. H. (see Fig. 1), No. 28130, was first seen in the Out-Patient Department in 1920 at the age of 19, at which time she complained of lack of sexual development and of retardation of growth. However, very little data were obtained at that time and it was not until 1930 at the age of 29 that any comprehensive studies were made; these led to the faulty diagnosis of panhypopituitarism. She stated that she had always been small and had never been strong.

In 1930 she was 4 feet 6 inches and weighed 74 pounds; her span was 7 cm. greater than the height. There was no breast development and the external genitalia were infantile. She had a small amount of axillary and pubic hair. She was definitely undernourished and her facies suggested premature old age as so often is seen in panhypopituitarism.

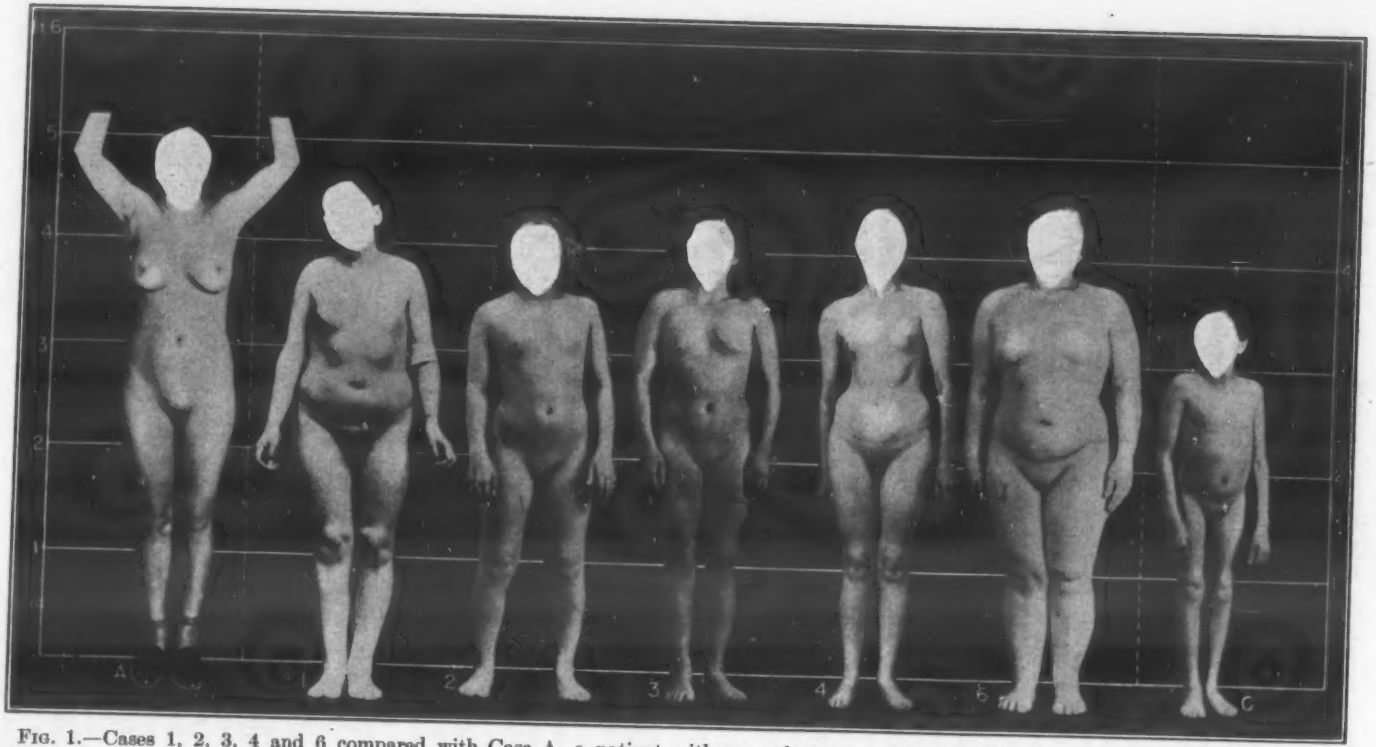

FIG. 1.—Cases 1, 2, 3, 4 and 6 compared with Case A, a patient with normal stature and acquired panhypopituitarism, and Case C, a patient with congenital panhypopituitarism. Case histories of Cases A and C (M. G. H., No. 160451 and 189660 respectively) were abstracted in a previous publication.[1] The breast development and large amount of pubic hair of Cases 1 and 4 are the result of estrin therapy.

The picture was further complicated by the development of grand mal seizures at the age of 28. These brought up the question of hypoglycemia, which is so often found in conjunction with panhypopituitarism. Her basal metabolic rate tended to be low, about −13%. Her serum calcium was 11.5 mg. per 100 cc.; her serum phosphorus 4.3 mg. per 100 cc. A Roentgen ray of her spine showed deformities in many of the vertebræ and some wedging, interpreted as "epiphysitis" (*cf.* Case 3).

The patient entered the hospital again in 1940 because of a detached retina resulting from a grand mal seizure. The correct diagnosis was then arrived at, when it was found in the insulin tolerance test that she was not hypoglycemia unresponsive, when the FSH test turned out to be positive for 10 mouse units per 100 cc., and when the 17-ketosteroid assays showed values in the neighborhood of 2 and 3.2 mg. per 24 hours. Roentgen ray films taken at the age of 29 and again at the age of 39 showed union of all epiphyses except the crest of the ilium which was not united even at the age of 39. The serum cholesterol was 197 mg. per 100 cc.

Case 5. E. C., No. 47830, was first seen at the age of 16 because she had never menstruated. She did not know when growth had become retarded. She had been a full term baby weighing only 4 pounds at birth and had always been sickly. Other members of her family were normal in height. She had developed a small amount of pubic hair at the age of 14.

On physical examination at the age of 21 (see Fig. 3) she was poorly developed and nourished; her height was 4 feet 7½ inches with her span 10.7 cm. greater than her height; her weight was 76 pounds. Her breasts were not developed at all and the external genitalia were infantile; the uterus was not made out by rectal examination; there was a small amount of pubic hair. The blood pressure was always elevated, circa 150/110; there was no other evidence of coarctation of the aorta, however.

She was operated upon at the age of 23 for intestinal obstruction from adhesions. A small amount of fluid was found in her peritoneal cavity at that time. Her uterus was found to be very small, cervix being two or three times the size of the fundus; the ovaries were present but less than 1 x 0.3 x 0.3 cm.

Roentgen ray films at age of 20 showed at least 5 years delay in bone age; at 26 they showed union of all epiphyses except those of vertebræ. The FSH test for 10 mouse units per 100 cc. of urine was repeatedly positive.

During October, 1937, the patient was started on large doses of estrin therapy (circa 1.5 mg. of estradiol benzoate intramuscularly twice weekly with intervals without therapy to allow for estrin-withdrawal-bleeding). It was noted that her strength and weight increased markedly with this therapy and receded when the therapy was omitted. She developed a large amount of axillary and pubic hair and considerable breast development (see Fig. 3). The 17-ketosteroid assays varied from 1 to 3.3 mg. per 24 hours after 2 years of large doses of estrin; after an additional 1½ years of large doses of estrin and progestin therapy these values rose to a range of about 8 to 11 mg. per 24 hours. With the addition of progestin therapy starting July, 1940, there was a further increase in her well-being.

Case 6. M. K., No. 144936, was first seen in 1938 at the age of 28. She had never had a menstrual period and had not developed sexually; she had been born at full term and had always been stocky in build. She believed that pubic hair had developed between the ages of 12 and 16. Other members of the family tended to be of short stature.

On physical examination she was 4 feet 7 inches with a span 7 cm. greater than her height; she weighed 146 pounds and was very sturdy (see Fig. 1). She had a slight amount of pubic hair and practically no axillary hair; her breasts resembled those of a girl in adolescence and consisted mostly of fatty tissue; external genitalia were infantile; cervix was very small as felt per rectum. Blood pressure was 134/86.

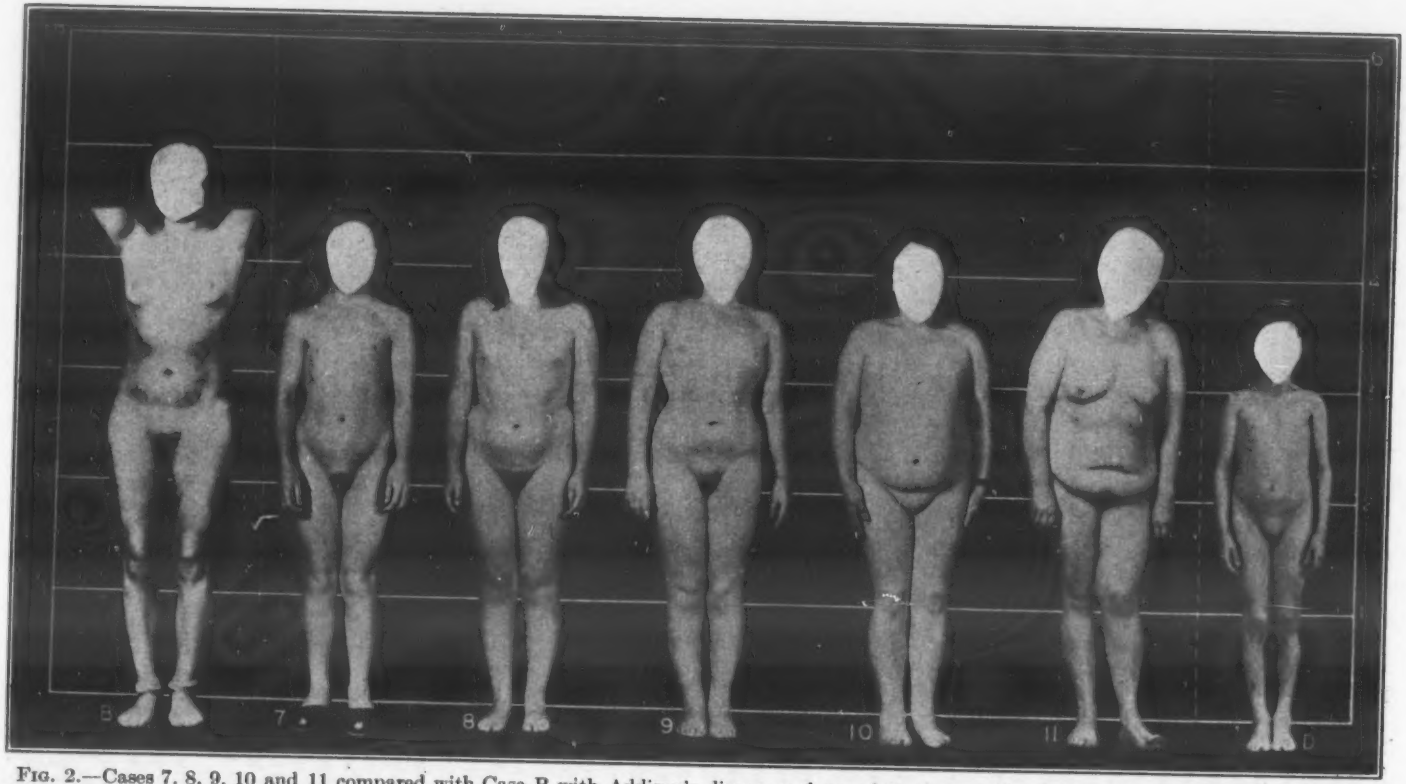

FIG. 2.—Cases 7, 8, 9, 10 and 11 compared with Case B with Addison's disease and complete absence of axillary and pubic hair (see text) and Case D (M. G. H., No. 210582) with congenital panhypopituitarism. The apparent breast development in Case 11 is due to fat deposits and not to breast tissue.

Several FSH tests for 10 mouse units per 100 cc. of urine were positive; two 17-ketosteroid assays were 5.1 and 4.5 mg. per 24 hours respectively. The Roentgen ray films of the bones taken at the age of 28 showed union of all the epiphyses. An insulin tolerance test was not abnormal. Two basal metabolic rates were +3% and +15% respectively. On peritoneoscopic examination the uterus was found to be infantile; the right tube was seen, but nothing but the slightest amount of tissue was seen in the region of the ovary; on the left side neither tube nor ovary was seen.

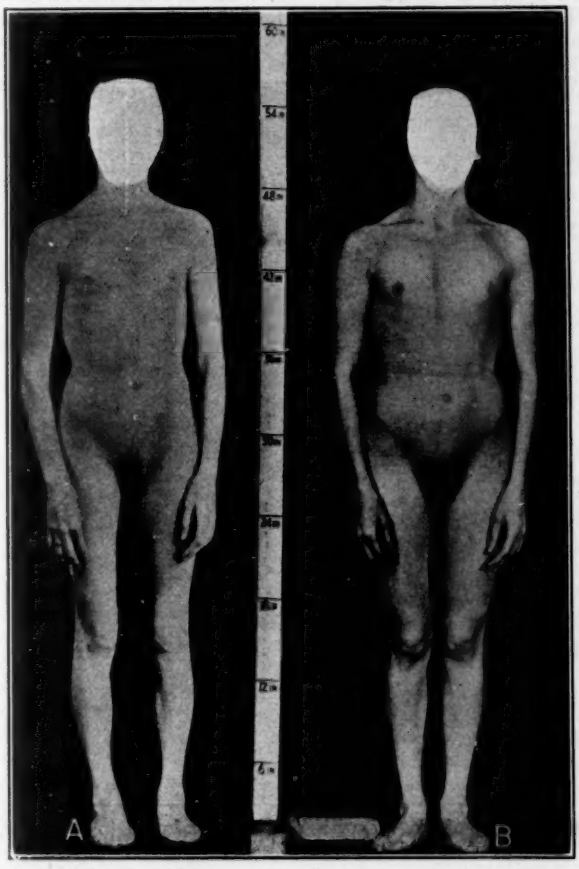

FIG. 3.—Case 5 before estrin therapy (*A*) and after estrin therapy (*B*). Note marked increase in pubic hair; note also increase in breast development which was more marked than suggested by the photograph.

CASE 7.—J. C., No. 296226, was first seen at the hospital in 1941 at the age of 14. Retarded growth had first been noted at the age of 8. At the age of 10 she had undergone an operation at the Children's Hospital in Boston for bilateral congenital webbing of the neck. Between November, 1938, and September, 1939, she had been treated with small doses of thyroid ($\frac{1}{2}$ to $\frac{3}{4}$ gr. daily) at the Children's Hospital; larger doses had led to symptoms of toxicity; during that time she had gained $1\frac{1}{4}$ inches in height

and 5 pounds in weight. Other members of the family were of normal stature.

On physical examination she was 4 feet 5 inches, with a span 1 cm. greater than her height; she weighed 71 pounds and was very sturdy (see Fig. 2). There was no breast development; the external genitalia were infantile; there was a small amount of pubic hair and no axillary hair. She showed scars on either side of the neck where the webbing had been removed; there was a marked increase in the "carrying angle" of the arm (*vide infra* [Fig. 4]). She had moderate hypertension, 146/88, which led to the suspicion on the part of our colleague Dr. William Parson of coarctation of the aorta. This was confirmed by Roentgen ray examination.

FIG. 4.—Photograph of Case 7 with Turner's syndrome to illustrate increase in "carrying angles" of arms.

Her bone age showed only slight retardation—greater than 1 year and less than 2 years. An FSH test for 10 mouse units per 100 cc. was positive; two 17-ketosteroid assays were 4.8 and 5.1 mg. per 24 hours respectively. The serum calcium was 11.6 mg. per 100 cc.; serum phosphorus 5 mg. per 100 cc.; serum phosphatase 6.4 Bodansky units.

CASE 8. A. G., No. 323961, was first seen at the hospital in 1941 at the age of 18½ years. (The authors wish to thank Dr. Z. Eileen Taylor for permission to study and report this patient.) Except that she had weighed only 4 pounds at birth her history until the age of 10½ was irrelevant. At that time she had suffered from a severe mastoiditis and bilateral otitis

media which had necessitated her being in bed 3 months. Following this illness her growth had become retarded; although she already had a slight amount of axillary and pubic hair at the age of 10½, further sexual development had not occurred; hot flashes had been noted for a short time following this. Her breasts had developed slightly under estrin therapy at the age of 16; she had also received a variety of other endocrine preparations without any marked benefit.

On physical examination she was short, 4 feet 7½ inches, with a span 1.1 cm. greater than her height; she was sturdy (see Fig. 2); there was almost no breast development but moderate amounts of axillary and pubic hair. As in Case 3 there was an increase in the "carrying angles" of the arms. Her blood pressure was 128/80. External genitalia were infantile.

Roentgen ray films showed that her bone age was more than 3 and less than 5 years retarded. An FSH test for 10 mouse units per 100 cc. of urine was positive; two 17-ketosteroid assays were 4.8 and 5.1 mg. per 24 hours respectively.

Case 9. Rh. F., was referred to one of us by Dr. Norman Popkin of Springfield, Mass., in November, 1941, at the age of 20 years. She had always been somewhat short, though otherwise well in childhood, and had not considered herself abnormal until the age of 15 when she had failed to menstruate. At that time she had been seen at the Evans Memorial Hospital where she had been given "pituitary tablets" and some injections. She had been again admitted in July, 1940, and had been discharged with the diagnosis of hypoplasia of the uterus, dwarfism,? hypopituitarism and with the recommendation that she be given estrin therapy. This had been started in November, 1940, and had been followed by a certain amount of uterine bleeding and increased development of the breasts. Since November, 1940, she had been taking 1½ gr. of thyroid daily, and since February, 1941, 3 gr. daily.

On physical examination she was 4 feet 9½ inches with a span 2.9 cm. greater than her height and like Cases 7 and 8 an increase in the "carrying angles" of her arms. Her weight was 112 pounds. She was sturdy (see Fig. 2); had well-developed axillary and pubic hair and slight breast development (see estrin therapy); external genitalia were poorly developed and uterus as felt by rectum was very small. She had an external squint of the left eye. Blood pressure was 140/90 without other evidence of coarctation.

Roentgen ray films showed a retardation of bone age of greater than 2 years and less than 4 years. Roentgen rays of the spine showed moderate osteoporosis and rather marked "epiphysitis" (see Fig. 5). An FSH test was positive for 10 mouse units per 100 cc. of urine and negative for 30 mouse units. Two 17-ketosteroid assays were 4.3 and 3 mg. per 24 hours respectively. The serum calcium was 12.5 mg. per 100 cc.; serum phosphorus, 3 mg. per 100 cc.; serum phosphatase, 5.6 Bodansky units. Repeat values were 11.1 mg. per 100 cc., 3.8 mg. per 100 cc. and 3.9 Bodansky units respectively. A 24-hour calcium excretion in the urine on a low-calcium diet was perfectly normal—61 mg.

Case 10. H. M., No. 329326, was first seen at this hospital in 1941 at the age of 37 years complaining of bilateral cataracts. She had always tended to be short; her breasts had never developed; she had never menstruated. She probably had had a cleft palate for which she had been operated on at the age of 10 years. She thought that she had not grown since that time. The cataracts had been present for 2 years. There was no family history of short stature, two brothers being over 6 feet.

On physical examination she was 4 feet 8¼ inches with a span 2.5 cm. greater than her height. She weighed 128½ pounds. She was well nourished (see Fig. 2) and looked at least 20 years older than she actually was. Thus, the skin on her face was slightly wrinkled and atrophic and she was

losing the hair on the top of her head (see Fig. 6). She had bilateral cataracts and well-developed Heberden's nodes (see Fig. 7). Blood pressure was 134/90. There was absolutely no breast development. External genitalia were infantile; she had practically no axillary hair and rather scanty pubic hair. Pelvic examination showed infantile organs but a slightly enlarged clitoris.

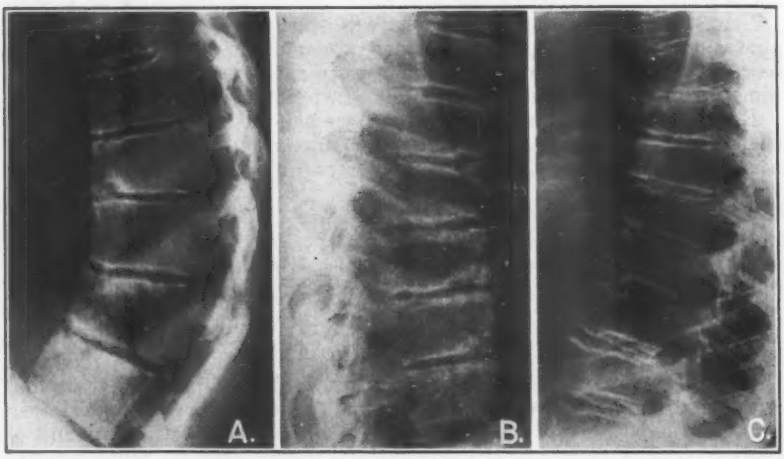

FIG. 5.—Illustration showing so-called "epiphysitis." *A*, Case 4. *B*, Case 9. *C*, Case 11.

FIG. 6.—Illustrations to show tendency of patients to exhibit senility. *A*, Case 4, age 40; *B*, Case 10, age 37; *C*, Case 11, age 30.

An FSH test for 50 mouse units per 100 cc. of urine was positive. Two 17-ketosteroid urinary assays were 4.9 and 6.6 mg. per 24 hours respectively. Roentgen rays showed closure of all epiphyses. There was generalized osteoporosis and considerable dorsal kyphosis with marked irregularity of the surfaces of the dorsal vertebræ, especially their anterior halves, and with considerable diminution in the depths of the vertebræ (see Fig. 5). Roentgen ray films of the elbows showed a peculiar underdevelopment of the external condyles of the humeri (see Fig. 7).

CASE 11.—J. A. M., No. 334333, was referred to this hospital in 1941 at the age of 30 by Dr. Vera Kinsey, with the diagnosis of diabetes mellitus and primary ovarian insufficiency. She had ceased growing at 12 and had never had a menstrual period; pubic hair had developed 2 years previously and axillary hair 1½ years previously. Diabetes had first been diagnosed at the New England Hospital for Women in November, 1941. She had had all the classical symptoms including polyuria, polydypsia and pruritus vulvæ; her initial fasting blood sugar had been 171 mg. per 100 cc.; she had responded well to insulin. During the past year she had developed unconscious episodes, in some of which she had hurt herself. There was no family history of short stature. The patient had been married for 12 years but had never become pregnant.

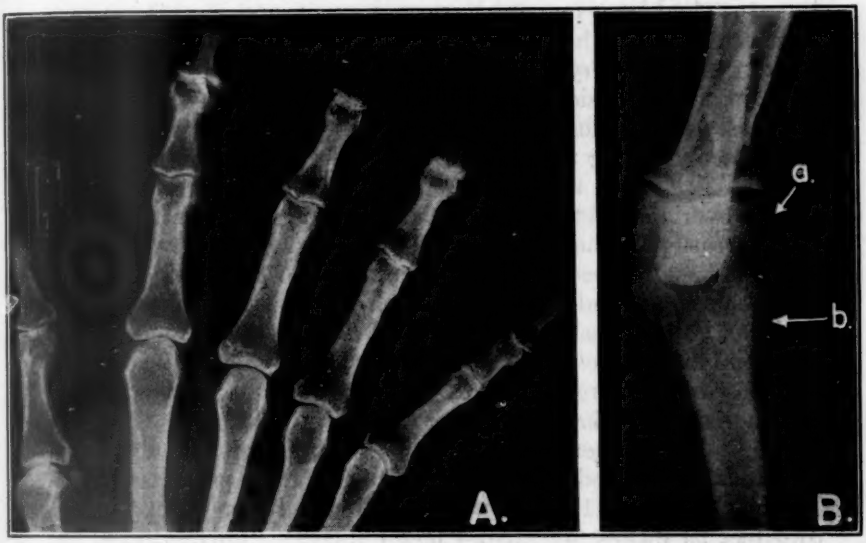

FIG. 7.—Roentgen rays on Case 10, age 37. *A*, Note changes in terminal interphalangeal joints characteristic of Heberden's nodes. *B*, Note lack of development of lateral aspect of head of humerus (*a*) and widening of humerus just above (*b*).

On physical examination the patient was 4 feet 8½ inches in height with a span 5.9 cm. greater than the height, and weighed 159¾ pounds. She was very obese; there was no breast tissue palpable, although at first sight because of large amounts of fat she appeared to have well-developed breasts (see Fig. 2). External genitalia were infantile; there was a small amount of axillary and pubic hair. Her facial appearance was that of a much older woman and the hair on the top of her head was beginning to thin out (*cf.* Case 10). Blood pressure was 136/100; there was no other evidence of coarctation of the aorta.

The FSH test for 10 mouse units per 100 cc. of urine was positive. Two 17-ketosteroid assays showed 0.6 and 2.7 mg. per 24 hours respectively.

Review of the Literature. Many features of the syndrome under discussion, exclusive to be sure of the important laboratory tests which assist in making the diagnosis *in vivo*, have been quite adequately set forth in the German pathologic literature. Olivet,[29] in

1923, reported an autopsied case with congenital absence of the ovaries. He emphasized the small stature (148 cm.) and the presence of axillary and pubic hair, in spite of absence of other secondary sex development. Pich,[32] in 1936, summarized the literature to that date and added 2 (Cases 1 and 3) interesting cases. Of the cases which were cited by Pich exclusive of Olivet's case, the authors feel that only four[33,34,35,36] surely belong to the syndrome in question. In the absence of the laboratory tests it is obviously difficult to separate this syndrome from certain other conditions.

As to diagnosis *in vivo*, mention of the syndrome was made in a previous paper from this clinic[15] before the references in the German literature had been found. Varney, Kenyon and Koch[48] independently recognized the syndrome and reported on several cases in May, 1941, and very kindly invited the authors to present their cases in the discussion. This was done by one of us (P. H. S.). The cases of the Chicago group were later reported;[49] the first 2 undoubtedly belong to the syndrome under discussion, the second 2 in all likelihood represent examples of decreased rather than absent ovarian function. These authors also called attention to another case published by Tronci.[46]

Discussion. *Decreased Stature.* One of the most surprising features of the syndrome under discussion is the decreased stature. These patients, however, can hardly be called dwarfs. Pich[32] emphasized this point and applied the word "Minderwuchs" (decreased stature) as opposed to "Zwergwuchs" (dwarfism); unfortunately the English language does not have one word for the translation of "Minderwuchs." One rather extraordinary feature about the decreased stature is the marked uniformity in size that these patients exhibit. The heights in the 11 cases here reported varied from 4 feet 5 inches to 4 feet 9½ inches (average, 4 feet 7 inches). Furthermore, the shortest patient in the series, who was 1 inch shorter than any of the other patients, has not yet attained her full height; the tallest patient in the series is 1 inch taller than any of the other patients.

The exact cause of the decreased stature remains problematical. In the final analysis the height which a person reaches depends on two factors: (*a*) the rate of growth, and (*b*) the length of time during which the individual grows. In this condition, since there is a delayed union of the epiphyses and hence an increase in the time during which the patients grow, the disturbance is obviously in the rate of growth.

There are five possibilities which seem worth discussing in regard to the cause for the decreased rate of growth.

The first possibility is that estrin may have a direct effect on the rate of growth in the epiphyseal cartilage. Estrin does cause proliferation of cells in many tissues; furthermore, there is a marked propensity for atrophy of tissue after the menopause (*cf.* postmenopausal osteoporosis and atrophy of the skin[3]). Zondek,[58] on

the other hand, produced dwarfism in animals by large doses of estrin. To be sure the *modus operandi* there was presumably an inhibiting action on the anterior pituitary; but, had there been any direct effect of estrin on the epiphyseal cartilages, one would have expected to have seen a temporary spurt of growth. Bogart, Sperling, Barnes and Asdell,[7] moreover, found that oöphorectomized rats grow more rapidly than normal female rats. Furthermore, in that syndrome discussed below, where estrin is equally diminished but where the primary fault is a lack of gonadotropic hormone production in the anterior pituitary in the absence of other pituitary insufficiency, one finds normal heights. We think it is unlikely that changes in growth are due to a direct effect of estrin on the epiphyseal cartilage.

The second possibility is that a primary ovarian deficiency leads to secondary changes in the anterior pituitary which in turn interfere with the production of growth hormone by said gland. Thus it is possible that a gland which is producing a large amount of FSH might be less able to produce growth hormone. The autopsy cases summarized by Pich[32] did show minor changes in the histology of the anterior pituitaries, some cases showing an increase in the eosinophil cells and some an increase in the chromophobe cells. Against this hypothesis is the fact that castration in males does not lead to decreased stature in spite of the fact that the same overproduction of FSH in the pituitary takes place. The authors do not favor this explanation of the decreased stature.

A third possibility is that the decrease in estrin production leads to a secondary change in the adrenal cortex which in turn results in a decreased growth rate. There are many pieces of circumstantial evidence which rather lead the authors to favor this point of view. In the first place, testosterone is an important growth hormone; the adrenal cortex produces some steroids very similar to testosterone; tumors of the adrenal cortex lead not only to sexual precocity but to marked somatic precocity; ergo, anything that might affect adrenal cortical function might affect growth. Secondly, there is a marked spurt in growth in adolescent females at the time of puberty; concomitantly the 17-ketosteroid excretion in the urine, which is an index of adrenal cortical function, rises. Thirdly, in the condition under discussion associated with decreased stature the 17-ketosteroid excretion remains at about the level found in the prepuberty normal individual, suggesting that there is a decrease in adrenal cortical function as compared with the normal. Fourthly, there is considerable evidence that estrin stimulates some hormone of the anterior pituitary which in turn stimulates the adrenal cortex. Indeed, the authors attribute the rise in 17-ketosteroid production in females at puberty to this interrelationship. A hypothetical diagram illustrating the above-mentioned relationships is presented in Figure 8 and discussed below under "Pathologic Physiology."

A fourth possibility was suggested by Pich,[32] namely that the decreased stature was due to an associated thymus insufficiency. In her first 2 cases with marked decrease in stature she found marked involution of the thymus, whereas in the third case where there was less decrease in stature the thymus was normal. We have no comments to make on this hypothesis.

A fifth possibility is that the decreased stature has nothing to do with the ovarian hypofunction but that both are the result of some widespread defect in the organism. The frequency with which other congenital anomalies are met with in this condition would be a point in favor of this hypothesis.

The data to date are suggestive that estrin therapy accelerates growth in this condition; thus Case 7 grew 1 inch in 6 months under estrin therapy, whereas during the previous $2\frac{2}{3}$ years she had grown 3 inches. If it can be established that estrin does stimulate growth, possibilities 4 and 5 enumerated above could be eliminated.

Bone Age. All our patients showed evidence of delayed union of the epiphyses and most exhibited eunuchoid proportions, *i. e.*, the long bones were out of proportion to the rest of the body. Thus the span in each instance was greater than the height. The normal individual of average height, of course, tends to have a span which is equal to his height; the normal individual of short stature tends to have a span which is less than his height. Therefore, when one finds a short individual with a span greater than the height, it is strong evidence that the epiphyses were late in closing.

There is considerable individual variation in this group as regards bone age. In most instances, however, the retardation was not so great as one sees in pituitary dwarfism. Thus, in 5 patients (D. W. S., age 28; M. K., age 28; H. M., age 37; U. H., age 39; J. A. M., age 30) the epiphyses were closed; this statement does not apply to the crest of the ilium which was noted to be still open in patient U. H. at the age of 39. C. M. at the age of 22 showed the greatest retardation of the patients in our group; thus her bone age was estimated to show a retardation of greater than 7 years and less than 8 years. J. C., on the other hand, at the age of 14, had a bone age which showed a retardation of more than 1 year and less than 2 years. The patient of Roessl and Wallart[35] had open epiphyses at 39.

Just why the epiphyses should be less delayed in closing in ovarian insufficiency as opposed to panhypopituitarism is not clear; but it may very well be connected with the fact that the ovarian cases have normal or potentially normal adrenals, whereas the pituitary dwarfs have hypoplastic adrenals.

Patients With Primary Ovarian Insufficiency and Primary Amenorrhea but Without Short Stature. One does encounter instances (2 cases in our Ovarian Dysfunction Clinic) where a patient has never had a period (so-called "primary amenorrhea") and has little or no breast development, where the FSH test is persistently posi-

tive for at least 10 mouse units per 100 cc. of urine, but where one does not encounter short stature. Some of these cases, if not all of them, especially where there is slight breast development, may be explainable on the basis of a "premenarchal menopause præcox." Thus, the menopause may occur at any age; in some instances it occurs just after the menarche; there is no reason to believe that it might not occur just before puberty. If such were the case one might have a normal premenarchal adolescence with normal growth; ovarian failure might then take place at about the time the periods were to be established. This would lead to non-union of the epiphyses; the net result might even be slightly increased growth.

The above explanation is not very satisfactory for those cases where there is absolutely no breast development. The normal female adolescent child has considerable breast development several years before the establishment of the menarche.

Pich[32] correlated the relatively normal size (156 cm.) of her third case with the fact that the thymus was not as atrophied as in most cases. This is a possible explanation.

If one believes, as the authors rather do, that the short stature is related to a slight accompanying underfunction of the adrenal cortex, one might hypothesize that in certain cases this underfunction does not take place. It is of some interest that the 2 cases without short stature had slightly higher, albeit not significantly higher, 17-ketosteroid assays (5.3 and 4.7 mg. per 24 hours in 1 case; 7.5 and 5 mg. per 24 hours in the other) than 10 of the 11 cases of short stature (range: 1 to 5.1 mg.; average, 3.8 mg. per 24 hours*). The 17-ketosteroid excretions on Case 10, however, were 4.9 and 6.6 mg. per 24 hours. Finally, both the cases without decreased stature had more axillary and pubic hair than most of the untreated ones with short stature. Since this hair is probably an indication of adrenal cortical function (*vide infra*) this finding would point in the same direction.

Axillary and Pubic Hair. As stated above, the patients with the syndrome under discussion tend to have small amounts of axillary and pubic hair as opposed to pituitary dwarfs in which such hair is entirely absent. This brings up the question as to what is the direct cause of such hair growth in females. The fact that it grows out during puberty has led to the assumption that it is directly due to some ovarian hormone. If such were the case it is difficult to see why the patients with primary ovarian failure should have any such hair growth at all. The authors rather believe that the immediate hormone which stimulates growth of hair in these regions comes from the adrenal cortex.

In favor of this thesis that axillary and pubic hair are due to

* One value of 15.3 mg. per 24 hours was discarded on Case 8 as almost surely wrong.

adrenal cortical rather than ovarian function are the following considerations:

1. The 17-ketosteroid excretion, which is an index in females of adrenal cortical function,[15] rises at puberty, showing that there is a change in the function of the adrenal cortex as well as of the ovaries at that time; therefore, *a priori*, changes at that time might just as well be attributed to adrenal cortical function as to ovarian function.

2. Pituitary dwarfs have no axillary or pubic hair (see Figs. 1 and 2), whereas the patients with the syndrome under discussion usually have moderate amounts; the adrenal cortices in the former cases are atrophied, in the latter they are relatively normal.

3. Patients with the syndrome have less than the normal amount of axillary and pubic hair; the 17-ketosteroid excretion in these patients, while present, is subnormal.

4. There are four conditions in women which lead to loss of axillary and pubic hair; these four conditions are panhypopituitarism or Simmonds' disease, Addison's disease, hypothyroidism, and extreme old age; the 17-ketosteroid excretions are extremely low or absent in all four of these conditions.[15]

5. The authors have quite clear evidence that testosterone has a direct effect on axillary and pubic hair; since the adrenal cortex produces a hormone very similar to testosterone, if not testosterone itself, this is another reason to believe that the adrenal cortex effects axillary and pubic hair growth.

6. That ovarian function *per se* is not important to the maintenance of axillary and pubic hair is the fact that there is very little change after normal or artificial menopause in its growth.

7. Castration in adult males leads to a diminution of pubic hair toward the configuration of that seen in normal females; the axillary hair diminishes but usually does not disappear; prepuberty castration in males does not prevent the development of axillary and pubic hair which reaches a degree not dissimilar to that seen in normal females; since the castrated male still has a normal adrenal cortex, the above findings are consistent with the hypothesis under discussion.

8. The authors have studied a patient with Addison's disease who underwent a normal menarche with regular periods but who never developed any axillary or pubic hair (see Fig. 2, Case B). Her history is abstracted below under "Case B."

9. Estrin therapy to pituitary dwarfs has no effect on the status of axillary and pubic hair; with the same therapy to patients with the syndrome under discussion there is a marked increase in axillary and pubic hair; since estrin therapy is thought to stimulate the adrenal cortex *via* the pituitary these observations become explicable.

On the other hand, it is of interest that in many of these cases development of axillary and pubic hair occurs at about the time for

normal puberty; in some instances its appearance is distinctly retarded; in Case 11 it did not appear until the age of 28. The development of axillary and pubic hair at about the normal time for puberty in these cases suggests that the factor which normally sets off the stimulation of the ovaries by the pituitary at puberty leads at the same time to stimulation of the adrenals by the pituitary; in the condition under discussion because of lack of the ovaries one sees only the adrenal component. These observations in themselves would suggest that the increase in adrenal activity at puberty was not dependent on estrin production.

Addison's Disease With Absence of Axillary and Pubic Hair. CASE B (see Fig. 2). H. M., No. 210582, was first seen at this hospital in 1939 at the age of 21 years. She presented the classical picture of Addison's disease with pigmentation, hypotension, low serum sodium and chloride, hypoglycemia unresponsiveness as shown by the insulin tolerance test, and absence of 17-ketosteroids in the urine. Addison's disease had been present for at least a year and probably longer as "she had always been weak."

Her periods began at the age of 16 years and stopped 1 year before admission. She had never developed any axillary or pubic hair (see Fig. 2), in spite of the fact that she was well developed otherwise. Height was 5 feet 1 inch.

Other Congenital Anomalies. Pich[32] called attention to the frequency with which other congenital anomalies are met with in this syndrome. In this connection it is very interesting that her Case 3 had a coarctation of the aorta as did our Case 7. This latter patient also had congenital webbing of the neck for which she was operated upon at the Children's Hospital.[24] It is of further interest that a patient recently reported by Ornstein[30] as a case of hypopituitarism also had coarctation of the aorta; from the data published the authors feel that there is little doubt that the diagnosis was primary hypoövarianism rather than hypopituitarism. Dr. Lawson Wilkins (Johns Hopkins Hospital) showed one of the authors a patient who in all respects fits the syndrome and who like Case 7 has both coarctation of the aorta and webbing of the neck. He called the authors' attention to "Turner's syndrome."[47] This latter author described 6 cases in women characterized by short stature, complete absence of breast development, in most instances slight amounts of axillary and pubic hair, congenital webbing of the neck, and increase in the carrying angles of the arms (cubitus valgus) (see Fig. 4). Unfortunately, there were no studies on excretion of follicle-stimulating-hormone, nor any data on which to base the presence or absence of coarctation of the aorta. Strong evidence that Turner's syndrome is due to ovarian insufficiency and not to panhypopituitarism was brought forth by E. P. Sharpey-Shafer.[43] He reported on the autopsy findings of a case which died of miliary tuberculosis. The endocrine glands, except the ovaries, showed no gross lesions. One ovary could not be found and the other was thought to have been destroyed by tuberculosis, as no active ovarian tissue was demon-

strated. No mention was made of the aorta. Two of Turner's cases had internal squints as did our Case 9. Case 11 in our series had had a cleft palate; Case 10 had an anomalous condition of the bones at the elbow (see Fig. 7).

Ovarian Pathologic Anatomy. From the German literature, summarized by Pich,[32] it is quite clear that most of these cases are suffering from a congenital absence or extreme malformation of the ovaries. Less often the ovarian lack may be due to inflammatory disease at an early age. In Case 1 the question was raised, but not verified, that the ovarian lack might have been the result of destruction of the ovaries by Malta fever. Case 5 in our series showed rudimentary ovaries on gross inspection during an operation for appendicitis; they were reported as being less than 1.3 x 0.3 x 0.3 cm. in size. Cases 3 and 6 were examined with a peritoneoscope without finding any definite ovarian tissue. In those cases where there is a coarctation of the aorta it seems possible that the ovarian insufficiency may in some way be connected with faulty blood supply.

Precocious Senility. From an academic point of view one of the more interesting features of this weird syndrome is the marked tendency to precocious senility reminiscent of that seen in panhypopituitary dwarfs where the term "progeria" has been applied. In a previous communication from this laboratory[3] attention has been called to the marked tendency of women after the menopause to develop osteoporosis and atrophy of the skin. It would now appear that ovarian lack largely accelerates the aging process of atrophy in general; thus a patient of 30 with primary ovarian insufficiency may look almost as old as a woman 30 years after the menopause.

Our series contains 4 patients over 30 years, Cases 4, 6, 10 and 11, aged 40, 31, 37 and 30 respectively. All showed atrophy of the skin of the face and wrinkles similar to those seen in much older women (see Fig. 6). Case 10, furthermore, had senile cataracts, marked alopecia of the scalp and Heberden's nodes (see Fig. 7). Case 11 had mild diabetes similar to that seen in older women. Both Cases 4 and 10 had developed epileptic seizures, the exact significance of which is not apparent.

What effect estrin therapy will have on the premature aging remains problematical; it will undoubtedly inhibit its development; will it make it retrogress?

Osteoporosis and "Epiphysitis" of Spine. Several of the patients in this group have shown moderate osteoporosis especially of the spine and pelvis. When present it is very reminiscent of that seen in the postmenopausal state[3] and undoubtedly due to the same cause, namely ovarian insufficiency.

Many of the cases, notably Cases 3, 4, 9, 10 and 11, showed to a greater or lesser degree irregularities, locally termed "epiphysitis,"

on the upper and lower margins of the vertebræ (see Fig. 5). The exact nature of these changes remains obscure.

Pathologic Physiology. In this section an attempt will be made to elucidate the deranged endocrine pattern in the syndrome under discussion. Certain parts of this pattern are very clear; others are still most hypothetical. In Figure 8, *A* a tentative scheme of the normal interrelationships of certain hormones which pertain to the problem at hand is depicted; in Figure 8, *B* certain hypothetical alterations in these interrelationships in the syndrome under dis-

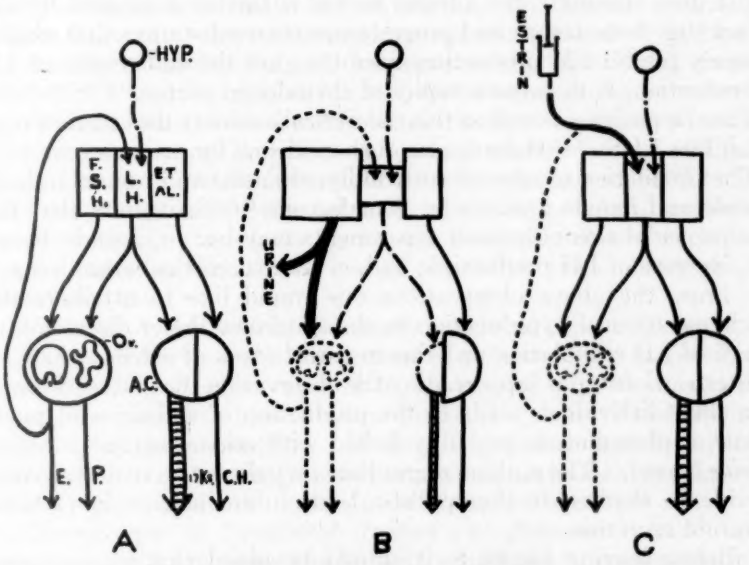

FIG. 8.—Hypothetical and schematic diagram illustrating possible hormonal interrelationships in (*A*) normal status, (*B*) condition under discussion, and (*C*) the condition under discussion under estrin therapy. The pituitary is divided into three compartments, that making follicle-stimulating hormone (*FSH*), that making lutenizing hormone (*LH*), and that making all the rest of the hormones, here designated "*et al.*" *Ov.*, ovary; *E*, estrin; *P*, progesterone; *A.C.*, adrenal cortex; *C.H.*, adrenocortical hormones which are not 17-ketosteroids; *17-KS*, 17-ketosteroids made from adrenal cortex; *HYP.*, hypothalamus. Dot-dash line connecting hypothalamus with pituitary indicates hypothalamic-pituitary nervous pathway partly controlling pituitary function. For further discussion see text.

cussion are set forth; finally in Figure 8, *C* a possible effect of estrin therapy on this hormonal imbalance is shown. The authors present these diagrams, not that they have much hope that they are correct in all their ramifications, but as a first approximation; it is hoped that others will make corrections.

That there is primary ovarian insufficiency in this syndrome there is little doubt. Thus, the autopsy findings in the German literature[32] and the high excretions of follicle-stimulating-hormone are strong evidence in this direction.[2] Furthermore, the low 17-keto-

steroid excretions make it quite certain that there is an accompanying disorder of the adrenal cortex.[15]

There is considerable evidence[9,12,13,16,19,20,23,26,39,50] that estrin stimulates either the luteinizing hormone (LH) of the anterior pituitary (see Fig. 8, *A*) or a closely related hormone (*vide infra*); there is also evidence that estrin administration causes hyperplasia of the adrenal cortex in female rats[39] and hyperplasia of the androgenic zones in male mice;[8,22] one is tempted, therefore, to hypothesize that the effect of estrin on the adrenal cortex is mediated through the LH function of the anterior pituitary (see Fig. 8, *A*). That LH does stimulate the adrenal cortex is further suggested by the fact that testosterone and progesterone, two substances that almost surely inhibit LH production since they are the end results of LH production, both cause atrophy of the adrenal cortex.[21,27,37,38,40,45,50] There is positive as well as this theoretical evidence that testosterone inhibits LH;[31,41,52] there is also such evidence for progesterone.[6,10,25] The production of adrenal cortical hyperplasias and tumors in both male and female animals by gonadectomy[11,17,44] suggests that the sequence of events in such experiments may be: *a*, gonadectomy; *b*, increase of LH production; and, *c*, adrenal cortical stimulation.

From the above observations one would like to attribute the adrenal cortical hypofunction in the syndrome under discussion to lack of LH stimulation and this in turn to lack of estrin. Such an interrelationship is supported by the observation that estrin therapy in these individuals leads to the production of axillary and pubic hair, a phenomenon probably linked with adrenocortical function (*vide supra*). The authors regret that they do not have unequivocal evidence that estrin therapy also leads to an increase in 17-ketosteroid excretion.

Before leaving Figure 8, it should be noted that it is so constructed as to suggest that LH stimulates only that part of the adrenal cortex which has to do with the production of 17-ketosteroids whereas the corticotropic hormone stimulates that part which does not produce 17-ketosteroids. There is really no evidence one way or the other on this point, but in a black and white diagram it is very difficult to hedge. This point is further discussed in a previous paper.[1]

It is now necessary to discuss some evidence which suggests that the above scheme may have to be modified. Until recently it has been assumed that LH plays a part in three phenomena: 1, the preovulatory spurt of growth of the ripening follicle; 2, ovulation; and 3, progesterone formation by the corpus luteum. Astwood[4] has performed some very convincing experiments suggesting that the actual production of progesterone by the corpus luteum is not mediated through LH but through the "luteo-trophic" hormone. It would appear, therefore, that many of the functions that have

been attributed above to LH may really be mediated through luteotrophin. Thus it may be luteotrophin and not LH which is stimulated by estrin. Such a thesis is supported by the fact that estrin therapy in rodents does not lead to corpora lutea formation but to increased size of corpora lutea and increased production of progesterone.[28,42] Furthermore, it may be luteotrophin which stimulates the adrenal cortex and not LH; this suggestion gains weight from the fact that preparations containing adrenal cortical hormone also contain luteotrophin. The above explanation would take care of the disturbing fact that crystalline LH in hypophysectomized animals apparently has no effect on the adrenal cortex.[5,18] There is some evidence, moreover, that estrin causes hyperplasia of the adrenal cortex only in the presence of a functioning corpus luteum;[39] it may be of some interest, therefore, that the only one of our patients who has had a definite rise in the 17-ketosteroid excretion under therapy is the one who received both estrin and progesterone (see Case 5). Finally if it turns out that neither LH nor luteotrophin stimulate the adrenal cortex then one will probably have to modify the scheme by having estrin stimulate the corticotropic hormone directly or one of the corticotropic hormones if there are two.

Figures 9 *A*, 9 *B*, and 9 *C* are constructed similarly to Figures 8 *A*, 8 *B*, and 8 *C*, to show the hormonal relationships in pituitary dwarfism (Fig. 9 *B*) as opposed to the normal (Fig. 9 *A*) and the effect of estrin therapy in this condition (Fig. 9 *C*). The illustrations speak for themselves. It should be noted that because of complete lack of pituitary function estrin therapy has no effect on the adrenal cortex, and, hence, no effect on axillary hair.

Classification of Congenital Ovarian Insufficiencies. At the expense of slight repetition the authors would like to enumerate four distinct clinical entities leading to "primary amenorrhea," namely: *a*, the syndrome under discussion; *b*, menopause occurring shortly before the menarche; *c*, panhypopituitarism; and, *d*, a selective underfunction of one or more gonadotropic hormones with secondary ovarian atrophy.

The first three of these conditions and their differentiation from one another require no further discussion. Needless to say, "*b*" is not a congenital ovarian deficiency but rather an acquired one.

The authors have studied 2 cases characterized by complete absence of ovarian function, primary amenorrhea, absence of short stature, absence of persistently high excretions of FSH, 17-ketosteroid excretions which are probably slightly low, small amounts of axillary and pubic hair, responsiveness of axillary and pubic hair to estrin therapy, and moderately delayed bone ages. The authors do not feel too dogmatic about this syndrome but are now in the process of studying more cases. The syndrome may be the

female counterpart of what has been called "eunuchoidism-with-negative-FSH" in males.[15] In any case, the one thing the authors feel quite certain about is that the condition is not primarily ovarian but secondary to some pituitary disturbance but not to a panhypopituitarism. An acquired amenorrhea, apparently due to absence of follicle-stimulating-hormone, is not uncommon; it was discussed by Albright and Halsted.[2]

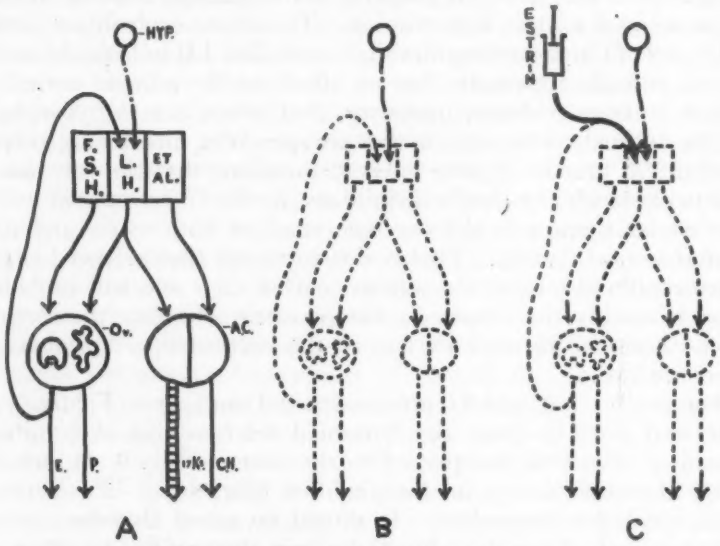

FIG. 9.—Hypothetical and schematic diagrams indicating possible interrelationships between various hormones in (*A*) normal status, (*B*) panhypopituitarism, and (*C*) panhypopituitarism under estrin therapy. For explanation see Figure 8; for discussion see text. Note that estrin therapy has no effect on the adrenal cortex because of absence of pituitary function.

Summary and Conclusions. 1. Eleven cases of a syndrome probably due to, and at least associated with, life-long ovarian insufficiency have been described.

2. This syndrome is characterized by infantile sexual organs, complete lack of breast development, small to moderate amounts of axillary and pubic hair in spite of complete absence of other so-called "secondary sex characteristics," short stature, the frequency of congenital anomalies especially webbing of the neck and coarctation of the aorta, late union of the epiphyses often accompanied by epiphysitis, osteoporosis, precocious senility, an excess of follicle-stimulating-hormone in the urine and a decrease but not an absence of the excretion of the 17-ketosteroids in the urine.

3. This condition is to be differentiated from pituitary dwarfism (panhypopituitarism) by the following criteria: *A*, The individuals

are short rather than dwarfs. *B*, The bone ages are only slightly retarded rather than markedly so. *C*, These patients have a reduced amount of axillary and pubic hair rather than none at all. *D*, Estrin therapy in these individuals leads to marked increase in axillary and pubic hair whereas it has no such effect in panhypopituitarism. *E*, These patients are quite strong and well nourished rather than weak and undernourished. *F*, The follicle-stimulating-hormone in the urine is increased above the normal rather than absent. *G*, The 17-ketosteroids in the urine are decreased but not minimal. *H*, In an insulin tolerance test these patients exhibit normal hypoglycemia responsiveness as opposed to hypoglycemia unresponsiveness.[48] These patients can have diabetes mellitus as a complication (see Case 12), whereas from the work of Houssay this complication is incompatible with panhypopituitarism.[46] *I*, These patients are prone to have other congenital anomalies.

4. The syndrome is differentiated from three other conditions causing life-long or primary amenorrhea; these are panhypopituitarism (pituitary, ateliotic, Lorain-Levi, or Paltauf dwarfs), "premenarchal menopause præcox," and a selective deficiency of the gonadotropic hormones of the anterior pituitary.

5. A discussion is included as to which hormones in females directly cause axillary and pubic hair growth; evidence is cited suggesting that this function in females depends on an adrenal cortical hormone.

6. Five hypotheses are discussed as possible causes for the diminished rate of growth in this syndrome; the authors rather believe it results from decreased adrenal cortical function which in turn results from decreased pituitary-stimulation-of-the-adrenal-cortex which in turn results from decreased estrin production.

7. Evidence is presented to suggest that Turner's syndrome—congenital webbing of the neck, sexual and somatic infantilism, and cubitus valgus—is a subform of this syndrome.

8. Emphasis is placed on a marked tendency to precocious senility in this syndrome; an analogy is drawn between the atrophied tissues after normal menopause and the atrophy exhibited by these patients at a very much younger age.

9. Replacement therapy with estrin leads to a marked increase in general well-being, causes development of the breasts and increase in axillary and pubic hair, and probably leads to an increase in the rate of growth in those subjects whose epiphyses are still ununited.

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"EPINEPHRINE SHOCK" AS A MANIFESTATION OF A PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA

REPORT OF A CASE WITH SUCCESSFUL REMOVAL OF THE TUMOR

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ALTHOUGH it is well known that the administration of large doses of epinephrine intravenously to the experimental animal will result in profound circulatory failure,[1,7,9] the development of shock-like symptoms in cases of pheochromocytoma in which there is presumably an excessive secretion of epinephrine or an epinephrine-like substance[2] has been noted only occasionally, and there has been little comment concerning its significance. Oberling *et al.*[14] describe the case of a 28-year-old female with a pheochromocytoma who had rapid fluctuations in blood pressure from 170/125 to 220/155 and who died in shock a few hours after delivery. Evan's case,[8] a 12-year-old girl, had 2 severe paroxysms terminally in which the blood pressure rose to 285/230 mm. and which were followed by marked tachycardia and circulatory collapse with a systolic pressure of 30 mm. The demonstration of a pressor substance in the blood closely resembling epinephrine in a case of pheochromocytoma[2] and the successful assays of the tumors for epinephrine strongly suggest that these shock-like states might be analogous to those produced in animals by the continuous intravenous infusion of epinephrine.[9] In only rare cases, however, have the paroxysms been of sufficient duration in humans to make possible careful observations of the effects of prolonged "epinephrine" discharge in the human.

The present case is an unusually severe instance of this syndrome in which the attacks were induced by the most simple physiologic stimuli for epinephrine discharge and in which the attacks lasted as long as 36 hours, often terminating with a clinical picture suggestive of so-called "epinephrine shock." Because of the alarming character and frequency of the attacks, the localization of the tumor and its successful removal presented unusual difficulties.

CASE HISTORY. The patient, a 23-year-old Puerto Rican girl, had enjoyed good health until 2½ years ago when she began to have episodes

of severe frontal and occipital headaches, accompanied by dizziness, weakness, epigastric, back and neck pain. Later these became more frequent and associated with a choking sensation, dyspnea, orthopnea, palpitation, blanching of the extremities and face, and sweating. These attacks lasted for about 15 minutes to a few hours, and were followed by a day of weakness, dizziness and mild headache. She had a severe attack $1\frac{1}{2}$ years ago, associated with marked dyspnea, orthopnea, and, apparently, collapse.

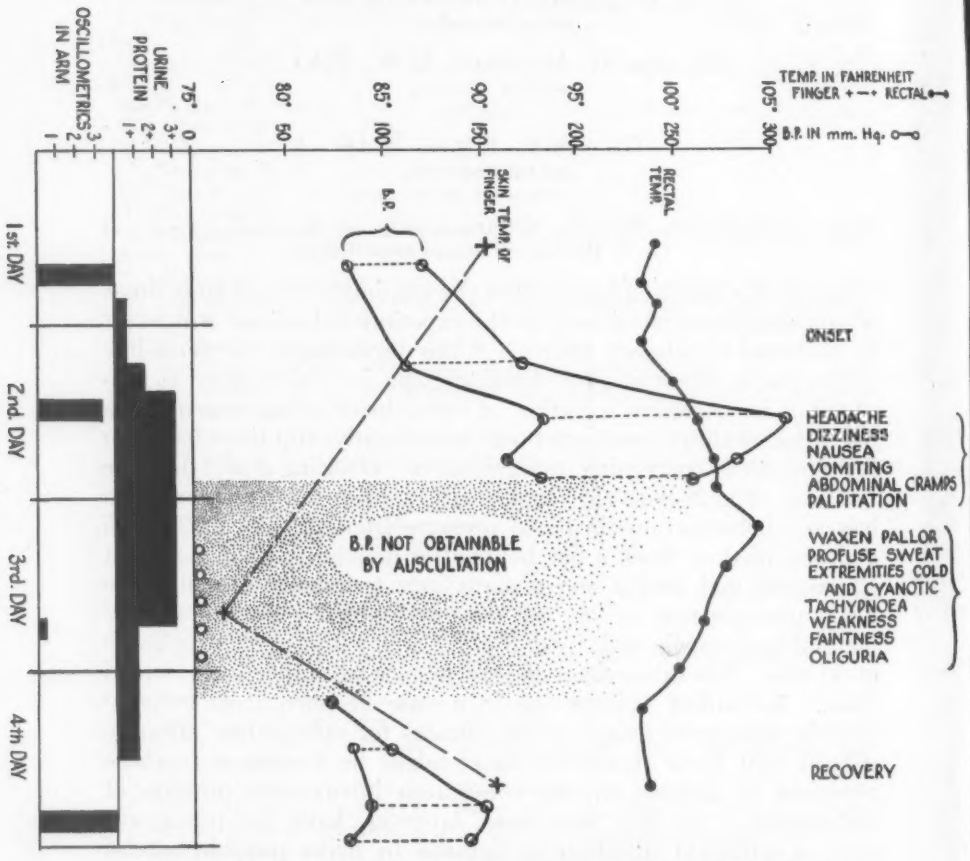

FIG. 1.—Observations during a typical paroxysm with circulatory collapse.

In a severe attack 11 months before admission, she was observed for 5 months at another hospital, during which period a number of typical attacks occurred. Because her blood pressure rose to high levels during attacks, a pheochromocytoma was suspected. During the first attempt at exploration of the left adrenal area, the induction of anesthesia precipitated a severe attack and a phlebotomy was performed because of the development of pulmonary edema. Subsequent exploration failed to reveal a tumor on the left side. Postoperatively she continued to have frequent mild attacks, although she was free of severe attacks for about 7 months. Ten days before admission a number of severe attacks occurred in rapid succession.

Physical examination revealed a frail, but fairly well-nourished girl with moderate pallor. The fundi showed slight narrowing of the arteries and somewhat hyperemic disks with indistinct margins. The heart was not enlarged. The peripheral arteries were slightly thickened. The abdomen was soft; no masses were palpable. The left biceps reflex was more active than the right; the right ankle- and knee-jerks were greater than those on the left. A left Hoffmann reflex was present. The blood count was normal. The urine showed a faint trace of albumin. The fasting blood sugar was 90 mg. per 100 cc. and urea nitrogen 14 mg. per 100 cc. Roentgenograms of the abdomen and chest showed no abnormalities. An intravenous pyelogram revealed the kidneys to be normal in size and position.

Description of a Typical Attack with Shock Syndrome. (Fig. 1.) During her stay in the hospital, the patient had frequent attacks, most of which were spontaneous and a few induced. The attacks varied in severity from lesser ones lasting an hour or more, to the most severe ones lasting over 36 hours. Between attacks her blood pressure was usually moderately elevated, ranging from 140 to 160 mm. Hg systolic and 90 to 110 mm. diastolic, but occasionally was entirely normal.

A sudden onset of palpitation, pounding headache, blanching of the face and extremities, abdominal cramps, nausea and repeated vomiting, was followed by marked diaphoresis. Blood pressure readings taken shortly after the onset showed extreme elevation, frequently over 310 mm. Hg systolic and 180 mm. diastolic. When the attack continued beyond 8 to 12 hours, during which period the patient continued to complain bitterly of pounding headache, palpitation, abdominal pain and vomiting, an interesting sequence of events ensued. The major peripheral vessels began to show evidences of progressive constriction, the pulses becoming of very small amplitude until entirely obliterated both to palpation and oscillometric determination (Table 1). At times constriction of the arteries was

TABLE 1.—OSCILLOMETRIC READINGS DURING AND BETWEEN PAROXYSMS

	Interval	Paroxysm
Right ankle	1.0	0
Right calf	1.5	0
Right thigh	2.5	less than 0.5
Left ankle	1.5	0
Left calf	3.0	0
Left thigh	3.0	less than 0.5
Right wrist	0.5	0
Right forearm	1.5	0
Right arm	4.0	less than 0.5
Left wrist	1.5	0
Left forearm	3.5	0
Left arm	3.0	less than 0.5

so great that even the pulsations of the carotid arteries were barely palpable and the pulse rate could only be obtained at the precordium. Because of the absence of audible or palpable pulsations, it became impossible to determine the blood pressure by means of the sphygmomanometer. The extremities, including the nose and ears, became extremely cold, pale, and cyanotic. The temperature of the skin, determined by the Dermatherm, showed a fall of as much as 7.6° C. in the extremities but little change over the trunk, while the rectal temperature rose to as high as 40°C. (104°F.). This gradient in skin temperature was a striking finding, repeatedly confirmed (Table 2, Fig. 1). Profuse diaphoresis over the trunk and face was always present at this time and there was usually a tachycardia, reaching

130 per minute. The neck veins sometimes appeared distended, and the patient often complained of dyspnea. The venous pressure in the antecubital vein, however, was found to be normal during the early part of one attack, and during a later stage collapse and constriction of the veins of the extremities was so great that venipuncture became impossible.

TABLE 2.—SKIN AND RECTAL TEMPERATURES IN DEGREES CENTIGRADE DURING AND BETWEEN PAROXYSMS

	Interval	Paroxysm
Right forefinger	32.3	24.7
Left forefinger	30.8	26.1
Right forearm	32.8	29.9
Left forearm	31.8	29.6
Right arm	32.8	30.4
Left arm	31.5	29.3
Right great toe	31.3	25.4
Left great toe	31.3	25.2
Right calf	30.8	28.4
Left calf	31.3	28.6
Right thigh	31.8	31.9
Left thigh	31.3	30.2
Abdominal wall	33.3	33.2
Sternum	33.3	31.4
Nose	31.8	24.4
Rectum	37.0	40.0

During the height of an attack the fundi showed definite changes, which were described by Dr. Lambert as follows: "In the supine position, with a blood pressure of 270/150, the arteries are somewhat thinner than normal with a bright irregular reflex and are quite irregular in calibre. They indent the veins somewhat and there is a general slight propulsive pulsation. The veins are also irregular in calibre, and are somewhat dilated. Examination after standing (blood pressure 305/170) showed what seemed to be a more general narrowing of the arteries, but no definite transitory or motile spasms could be detected."

Urinalyses during an attack regularly showed an increase in albumin to 3+, and the appearance of red cells, white cells and casts. Slight glycosuria was noted once. The blood sugar was not found to be elevated on the one occasion it was possible to do a venipuncture. Electrocardiograms during an attack showed a sinus tachycardia, high QRS, depressed R–T 1, 2 and 3 segments, and inverted T–1.

Eventually, after 24 to 36 hours, the patient showed evidences of peripheral vascular collapse, with apparent blood pressure readings obtained as low as 76/60 mm., hemoconcentration (as demonstrated by a hematocrit reading of 53%), tachycardia and torpor, while the evidences of diminished blood flow through the extremities persisted. The state of circulatory collapse would last several hours and then gradually the peripheral pulses would become fuller and slower, the extremities warm, the blood pressure would return to normal, the hematocrit would fall to its normal value of 38%, and the systemic temperature would fall, until the whole cycle was repeated with the next severe paroxysm.

Induction of the Attacks. The means to induce the attacks afforded interesting support for Cannon's concept of the emergency function of the sympathico-adrenal system.[5] The usual stimuli for sympathetic discharge were found to produce attacks readily. Spontaneous attacks occurred during fear, anger, excitement, sexual intercourse, before meals when the blood sugar was probably falling, and during the induction of anesthesia when asphyxia probably was a factor.

Similarly, attacks were induced by analogous procedures. A change from the prone to the sitting position resulted in a rise in blood pressure from 150/110 mm. to 175/125 mm. Standing then led to a prompt fall to 155/110 mm. and then a rapid rise to 305/170 mm. in 15 minutes, with a pulse rate of 80. Massage of the carotid sinus during this maximum rise caused a transient slowing of the pulse and a prompt fall in pressure to 160/115 which, however, immediately rose on discontinuing the stimulation, demonstrating the reflex pathways to be intact and at least potentially active. On reclining, the blood pressure returned to normal only after several hours (Fig. 2). This response to posture was regarded as an excessive exaggeration of the normal postural blood pressure reaction and correlated clinically with the patient's history of attacks upon arising in the morning.

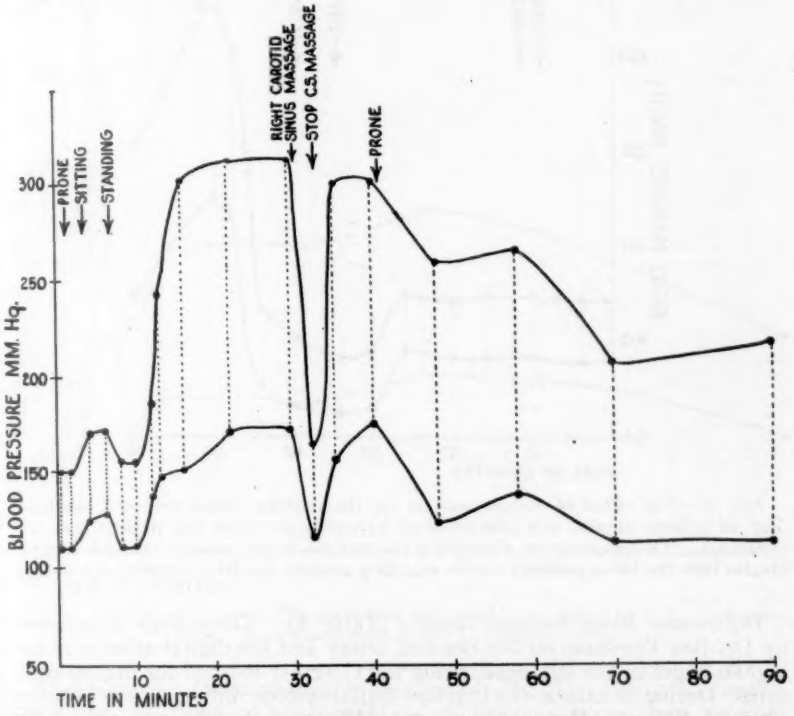

FIG. 2.—The effect of change in posture in a case of pheochromocytoma of the adrenal. Note the effect of carotid sinus stimulation.

To demonstrate that the postural reaction was not an emotional one, the patient was given 5 gr. of sodium amytal intravenously until she was asleep. During the administration of the drug the blood pressure fell from 120/90 to 94/40. The patient was then supported in the erect position and the blood pressure rose promptly to 270/160 (Fig. 3).

On another occasion, hyperventilation for 3 minutes caused a rise in pressure from 170/110 to 305/160, the pressure not yet returning to its initial value at the end of 1 hour. In this instance, mechanical massage of the tumor probably played a rôle, since at operation the tumor was found to be adherent to the diaphragm.

Cold and pain, induced by immersion of the hand in ice water for 2 minutes, caused a rise in pressure from 135/98 to 200/135 in 3 minutes, which was maintained for over an hour (Fig. 4).

Attempts to induce paroxysms by massage of the abdomen were uniformly unsuccessful. Studies with insulin, adrenalin, histamine and other drugs were not carried out because of the severity of the paroxysms. A dextrose tolerance test had to be omitted for the same reason.

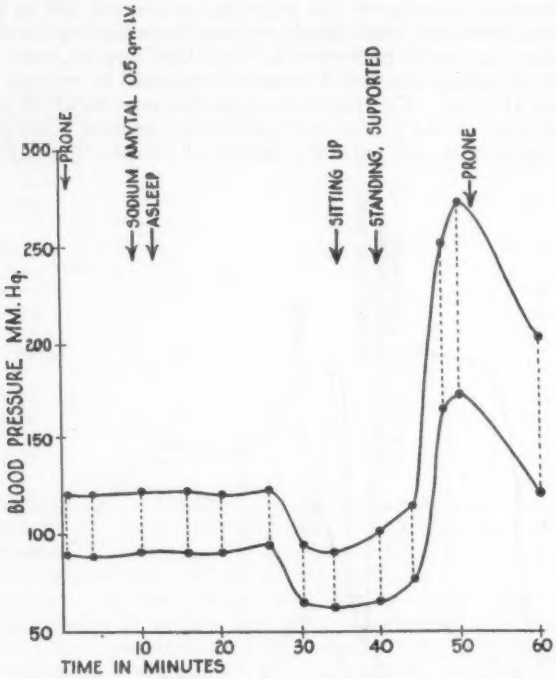

FIG. 3.—The effect of sodium amytal on the postural blood pressure response; 5 gr. of sodium amytal was administered intravenously until the patient was unconscious. The response on supporting the patient in the upright position demonstrates that the blood pressure rise on standing was not due to an emotional reaction.

Differential Blood Pressure Studies (Table 3). These were determined by Dr. Ben Friedman on the brachial artery and the digital arteries of the middle finger of the left hand, using the Gaertner method for digital pressures. During an attack, the brachial-digital systolic difference was between 100 and 120 mm. Hg, as compared to 50 mm. after the removal of the tumor, which is within normal limits. This high differential is characteristic of the hypertension produced by epinephrine.

TABLE 3.—BRACHIAL AND DIGITAL BLOOD PRESSURES (METHOD OF GAERTNER)

	During a paroxysm	After removal of tumor
Brachial systolic pressure (mm. Hg)	220	118
	260	110
	280	110
Digital systolic pressure (mm. Hg)	130	68
	154	60
	150	54
Brachial-digital systolic blood pressure difference	90	50
	106	50
	130	56

Treatment of the Paroxysms. All measures employed to terminate attacks were without avail. Ergotamine tartrate, which is an antagonist to epinephrine was completely ineffectual in a dose of 1 mg. intravenously. Sodium amytal and other rapidly acting barbiturates gave only slight symptomatic relief, but did not appear to shorten the attacks or lower the blood pressure, except transiently. It was felt that the use of parasympathetic drugs was contraindicated because of the sympathetic rebound likely to occur after their administration. The use of plasma during the shock-like states was considered, but did not prove possible because of the extreme collapse of the peripheral veins.

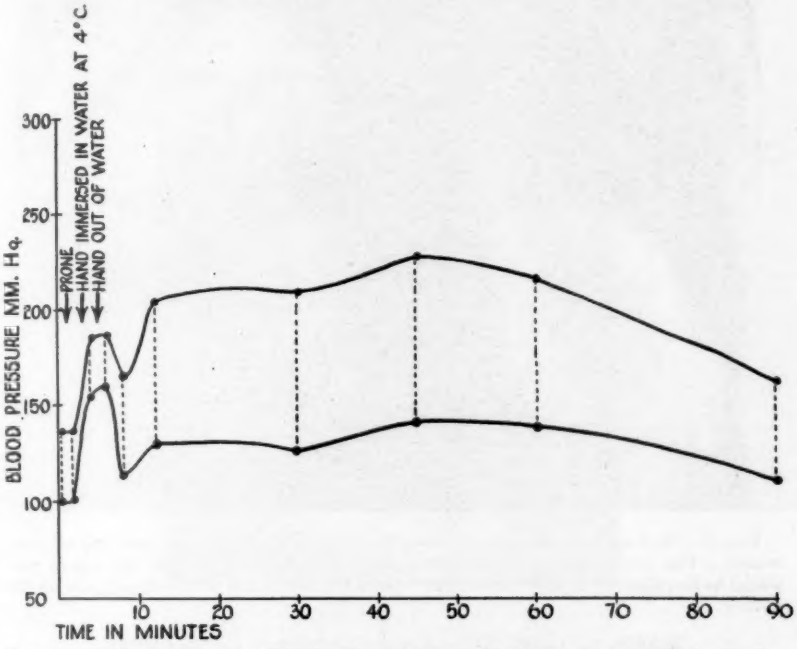

FIG. 4.—Cold pressor test. The hand was immersed in ice water at 4° C. for 2 minutes. Note the sustained rise in blood pressure.

Roentgenologic Demonstration of the Tumor (Fig. 5). Perirenal insufflation[15] was performed by the instillation of 550 cc. of oxygen into the right perirenal space. There was no untoward reaction. Roentgen ray examination revealed a suggestion of a small mass in the right adrenal area, the lower portion of which was flattened and caused a flattening of the upper pole of the kidney.

Preoperative Preparation. Because of the dangers of emotional excitement, preparations were made to "steal" the adrenal as is usually done with the thyroid in cases of Graves' disease. Avertin was given as the basal anesthetic. To avoid the inevitable shock attendant upon the removal of an adrenal tumor, the patient was given desoxycorticosterone acetate (synthetic adrenal cortical steroid) intramuscularly, and glucose and saline intravenously preoperatively, adrenal cortical extract intravenously during the operation, and epinephrine hypodermically and intravenously and epinephrine-in-oil intramuscularly during and after the operation. This régime, which has been previously outlined by Biskind *et al.*[4] was designed

to prevent the effects of the sudden withdrawal of epinephrine from the blood, which is the cause of the immediate fall in blood pressure on tying off the tumor, as well as the delayed shock which is probably due to temporary adrenal cortical insufficiency. Anoxia at the operation was minimized by the use of cyclopropane as the anesthetic.

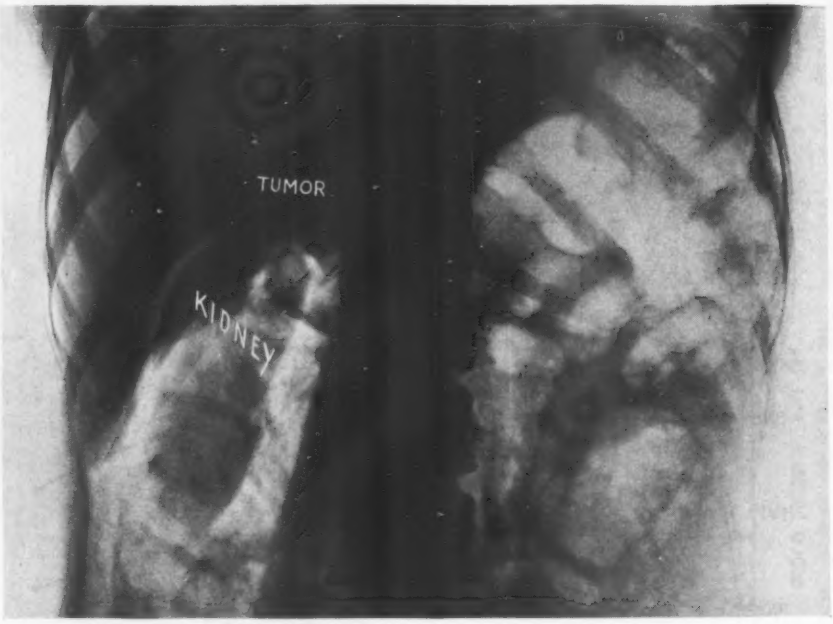

FIG. 5.—Perirenal insufflation showing the outline of the kidney and the adrenal tumor. The upper surface of the tumor was not delineated because the tumor was found to be adherent to the diaphragm. Note the flattening of the upper pole of the kidney.

Operation. Through a right lumbar incision the renal area was exposed, the kidney was mobilized and retracted downwards. A tumor the size of a large plum was found in the adrenal area. It was round, semi-soft, attached to the upper pole of the kidney and adherent to the diaphragm. At the onset of the operation, the systolic blood pressure was 120 mm. As soon as the tumor was palpated, the blood pressure rose to 220 mm. Hg, at which level the pressure was maintained almost constantly until the last vessel to the adrenal gland was ligated. At this point the blood pressure dropped precipitously to 110 mm. and then further to 70 mm. The tumor was easily removed.

LEGENDS FOR FIGS. 6, 7 AND 8

FIG. 6.—Gross appearance of the adrenal tumor. Scale in centimeters.

FIG. 7.—The tumor in section. Note the very thin section of adrenal cortex. The rest of the specimen represents the medullary tumor.

FIG. 8.—Microscopic section of the pheochromocytoma.

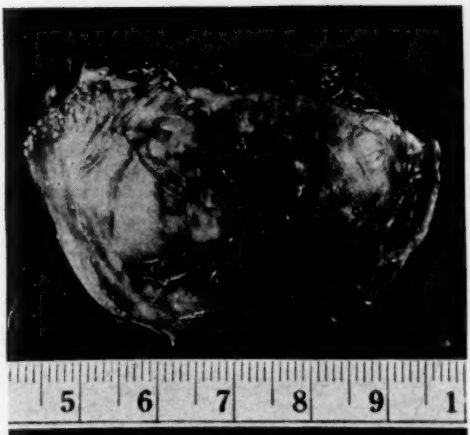

Fig. 6

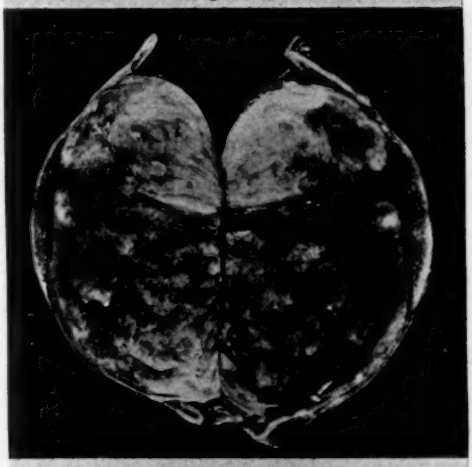

Fig. 7

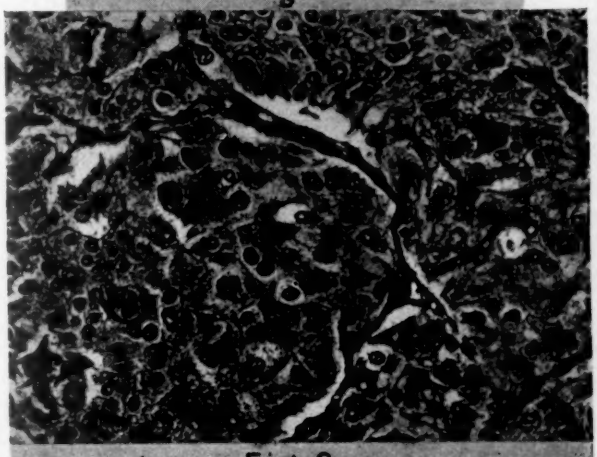

Fig. 8

(For legends see opposite page)

During the first 12 hours postoperatively, the blood pressure ranged between 70/50 and 90/65, but the patient's general condition remained relatively good. Thereafter, the blood pressure was maintained at about 100 mm. Hg systolic and her course was uneventful.

Pathology and Bio-assay (Figs. 6, 7, 8). The tumor was found to consist of a greatly enlarged adrenal gland, weighing 31 gm. and measuring 5.5 by 3.5 cm. On section the enlargement of the gland was found to be due to the presence of a tumor occupying the central portion of the gland and uniformly expanding it. The cortex was intact and was visible as a narrow golden yellow zone spread over the surface of the tumor. The central tumor was mottled grayish brown, soft and cellular, and when immersed in dichromate solution assumed a striking dark brown appearance. Microscopically it had the characteristic structure of a pheochromocytoma (Fig. 8).

Bio-assay of the tumor was performed by Dr. M. B. Bender, who found that each gram of tumor caused a reaction in the denervated cat's iris, a retraction of the nictitating membrane, and a blanching of the sympathectomized ear equivalent to that caused by 8 mg. of epinephrine. It also caused a rise in blood pressure in the cat.

Postoperative Studies. Postoperatively the patient became entirely free of spontaneous attacks. Hyperventilation and immersion of the hand in ice water caused no significant rise in blood pressure. Postural studies revealed a mild degree of postural hypotension 1 month after operation, but this disappeared later. Oscillometric readings and skin temperature readings became entirely normal. Subcutaneous injection of 0.007 mg. of epinephrine per kg. of body weight caused no significant rise in blood pressure. The electrocardiogram returned to normal. The urine showed only a very faint trace of albumin. A dextrose tolerance test revealed a fasting value of 65 mg., a rise to 125 mg. in 1 hour and a rapid fall to 45 mg. with hypoglycemic symptoms at 4 hours. There was no evidence of adrenal cortical insufficiency either by electrolyte studies or from the subsequent course. On examination 3 months after the operation, the patient had gained 20 pounds and was entirely asymptomatic. There was no postural hypotension at this time.

Comment. This patient, who had symptoms of hyperepinephrinemia for at least $2\frac{1}{2}$ years, had attacks of such unusual severity that she presented an excellent opportunity to study the effects of prolonged epinephrine discharge in the human. A review of the literature reveals few instances in which the paroxysms were of such long duration; and those which were terminated fatally. Pincoffs[16] reported a case in which the attacks lasted up to 10 hours. In Belt and Powell's case[3] spontaneous attacks lasted up to 6 to 7 hours, and the terminal paroxysm, which had many features similar to the case here described, lasted 48 hours and was characterized by marked hypertension, which gradually declined, tachycardia, persistent vomiting, hyperpyrexia up to 107° F., and finally death after a period in which the blood pressure fell and the pulses became barely perceptible. In most of the reported cases attacks lasted from only a few minutes to a few hours.

Hyperpyrexia, particularly during the terminal attack, is another manifestation which has been noted several times but has received

little comment. In one of the earliest cases to be recognized,[10] the patient had several paroxysms a day lasting from 1 to 4 hours with a blood pressure rise to 260/180 and fluctuations in temperature from 39.5° to 40° C. Belt and Powell's case had a temperature of 107° F. terminally and De Wesselow[6] reported that temperature rose to 105° F. preterminally, although he does not describe the clinical state at this time. In our case, every attack which lasted more than a few hours was associated with a rise in rectal temperature to 102° to 104° F. and a simultaneous fall in skin temperatures and oscillometric readings in the extremities. This rise in internal body temperature may be considered as due both to the increased heat output caused by epinephrine, which Cannon has found to amount to 50 calories per mg. of epinephrine,[5] and to failure to dissipate heat by normal channels at an equivalent rate because of the marked peripheral vasoconstriction and decrease in peripheral blood flow.

The occurrence of marked vasoconstriction in the extremities with subjective and objective coldness, has been noted in almost all cases and is a classical feature. Beer, King, and Prinzmetal[2] reported decreased skin temperatures and oscillometric readings during an attack and described unusual vasomotor changes in the extremities. MacKenzie and McEachern[12] mention inability to palpate the pulse at the wrist during an attack. Mayo[11] noted obliteration of the capillaries of the nail beds during attacks. In no reported case, however, did the vasoconstriction assume the remarkable degree it did in our case, in which all peripheral pulses became impalpable and remained so for many hours. The marked fall in skin temperatures in the extremities was another evidence of the striking decrease in blood flow during the paroxysm. These changes were associated with a subjective feeling of coldness and paresthesiæ and objectively by marked pallor and mottled cyanosis. The changes in the small vessels were also reflected in the fundus which presented a picture of constriction and propulsive pulsation in the arteries during the attacks.

The chain of events during a typical paroxysm terminating in a state of peripheral vascular collapse bears a striking resemblance to the phenomena which occur in animals receiving large doses of epinephrine intravenously. That massive doses of epinephrine can produce a fatal type of circulatory collapse is well known.[1,7,9] In a recent study, Freeman, Freedman and Miller[9] found that a continuous intravenous infusion of epinephrine into dogs at the rate of 0.0034 to 0.0164 mg./kg./min. for a period of 1 to 1½ hours resulted in a decrease in plasma volume and shock. When the epinephrine injection was started, the blood pressure rose rapidly to 250 to 320 mm. Hg, and the rate of blood flow through the paw decreased

to less than 1 cc. per 100 cc. of paw volume. The blood pressure then declined slowly, but was maintained throughout the period of injection at a level higher than normal, falling sharply when the epinephrine infusion was stopped. Usually within 10 minutes of the beginning of the infusion the mucous membranes of the mouth were seen to become pale and then cyanotic. At the end of 50 to 60 minutes the signs of clinical shock were marked. The extremities and ears were cold and had a doughy feel. The pulse was thready and the flow of blood in the ear veins slow and the blood dark. The rectal temperature rose rapidly. The hemoglobin rose and the plasma volume decreased by about 30%. The authors interpret the shock as the result of the severe reduction in blood flow resulting in anoxia in the peripheral capillaries, with consequent increased capillary permeability and loss of fluid and protein into the surrounding tissues. Due to progressive loss of plasma volume the vasoconstriction is unable to maintain the blood pressure which declines slowly. "The combination of loss of circulating fluids and peripheral vasoconstriction produce the clinical manifestations of shock. When the adrenalin is stopped and the blood-vessels allowed to relax, reflex vasoconstriction in response to the lowered pressure is insufficient to maintain adequate circulation to vital centers because of the fall in circulating blood volume." This mechanism also undoubtedly comes into play in the shock which almost invariably follows the surgical removal of these tumors. The close resemblance between this syndrome produced experimentally in dogs and the clinical picture presented by the patient cannot be overemphasized.

In the management of these cases the importance of pre- and postoperative care must be emphasized again. Before operation every care should be taken to avoid the excitation of an attack, particularly by the emotional stimuli attendant upon the preparations for operation. Biskind *et al.*[4] have recently discussed the rationale and value of the use of both adrenal cortical hormones and epinephrine in the management of these cases. On removing such a tumor not only is there a sudden release from what had been probably a high level of circulating epinephrine, but also a decrease in cortical tissue which may produce a temporary adrenal cortical insufficiency. Furthermore, Parkins *et al.*[15] have demonstrated that the circulatory collapse of epinephrine shock may be largely alleviated by the administration of adrenal cortical hormone. Our patient was primed with desoxycorticosterone and salt preoperatively and received cortin and epinephrine during and after the operation. Epinephrine in oil was used because of its prolonged action.

The transient development of postural hypotension after the removal of the tumor is of interest as a possible manifestation of a

temporary decrease in the capacity for peripheral vasoconstriction on assuming the erect posture. This reaction is essential to the maintenance of normal blood pressure on changing posture. Although this may have been merely the aftermath of the operation and the resultant enforced bed-rest an additional factor may have been a defective ability of the vessels to constrict in response to normal vasoconstricting stimuli after having been subjected so long to the intense vasoconstricting effect of epinephrine.

Summary. 1. A pheochromocytoma in a 23-year-old woman is reported. Symptoms had been present for 2½ years and were of increasing severity.

2. Spontaneous attacks of unusual length and severity occurred, often ending in a state of peripheral vascular collapse. A comparison between these attacks and the phenomenon of "epinephrine shock" in dogs is made and the physiologic significance of these discussed.

3. Attacks were precipitated by the most simple mechanisms for eliciting sympathetic discharges. The significance of these reactions is discussed.

4. The tumor was localized by perirenal insufflation and successfully removed. The importance of preoperative and postoperative management is emphasized.

5. Postoperatively the patient developed a transient postural hypotension and low sugar tolerance curve with hypoglycemia which are interpreted in light of the balance between the sympathicoadrenal and vago-insulin systems.

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CLINICAL EXPERIENCE WITH RADIO-PHOSPHORUS IN THE TREATMENT OF CERTAIN BLOOD DYSCRASIAS*†

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AND

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Through the courtesy of Dr. John H. Lawrence, of the Berkeley Cyclotron Laboratory of the University of California, we have, since March, 1941, been supplied with sufficient radio-phosphorus to treat a group which now comprises 38 patients classified as follows: Polycythemia vera, 8; chronic myelogenous leukemia, 5; chronic lymphatic leukemia, 4; acute leukemia, 4; Hodgkin's disease, 5; lymphosarcoma, 6; multiple myeloma, 1; reticuloendotheliosis, 1; reticulum cell sarcoma, 1; and metastatic carcinoma, 3.

The achievements of Dr. E. O. Lawrence and his co-workers[1] in the production of radio-active substances are well known. Suffice it to say here that radio-phosphorus, having an atomic weight of 32 and therefore designated as P^{32}, is produced by the bombardment of ordinary red phosphorus, whose atomic weight is 31, by very rapidly moving deuterons generated in the Cyclotron. The resulting material, converted into an aqueous solution of dibasic sodium phosphate, retains all the properties of ordinary phosphate, with the addition of radioactivity. An amount of material which emits 3.7×10^7 beta-particles of radio-activity per second is said to contain 1 millicurie of beta-radiation. Because of many complex factors it is difficult and misleading to attempt to equate the millicurie with the "r" unit of familiar usage. Roughly, however, it may be said that a 50 kg. man who absorbs and distributes equally throughout the tissues a single millicurie dose of radio-phosphorus will have the equivalent of 0.7 "r" whole body irradiation in 24 hours. As P^{32}, however, is handled by the animal organism like ordinary P^{31}, the distribution is never equal. It is quickly concentrated in bone-marrow, liver, spleen, bones, and so forth. Furthermore, as in other radio-active elements, there is constant breakdown and decay. P^{32} has a half-life of only 14.3 days, in contrast to radium and thorium which have half-lives of hundreds of years. Thus with P^{32} there is no danger of cumulative radiation effects. Finally, nearly 50% of any given dose is normally excreted during the first 6 days and excretion continues thereafter. Thus after 6 weeks no

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† As both authors left Philadelphia on active service before this report was received, it is published with slight changes for which they are not responsible.—Editor.

significant amount of radiation can be found in any tissue following a single administration of P^{32}.

Dosage and Methods of Administration. The material, in solution, may be administered orally or parenterally. Single oral doses have varied from 1 to 20 mc. Single intravenous doses have varied from 0.2 to 2 mc. Less than 3 gm. of sodium phosphate have been administered orally in each dose; less than 1 gm. when given intravenously. Oral administration is accomplished by mixing the required dose with equal parts of orange juice. The mixture is swallowed before breakfast (with all laxatives interdicted for 24 hours before and after).

Too much phosphate (*i. e.*, too great a volume of low potency P^{32}) may produce diarrhea. This is wasteful and should be avoided. The material when administered by mouth is, in our experience, pleasant to take and free from untoward reactions.

The solution used intravenously is the same as that given by mouth. It is sterilized and kept in a vaccine bottle. The first doses are usually small, 0.1 to 0.3 mc. If well tolerated, larger quantities (1 to 3 mc.) may be administered.

The frequency of administration of radio-phosphorus follows no set rule. Some individuals receive the drug once each week, others 3 or more times a week. Usually repeated small doses are preferable to the single large one. The total number of doses varies according to the hematologic and clinical status and response of the patient.

No severe immediate reactions to radio-active-phosphorus solution have been observed. One patient died within 24 hours of administration of the drug by mouth. We are reasonably certain that the drug did not cause the fatality. Two patients complained of symptoms which strongly suggested mild radiation sickness. In one, nausea developed 2 weeks after an intravenous injection. The second individual developed nausea within a few days. If these represent true radiation sickness, they must indicate a very marked sensitivity of the individuals concerned.

Polycythemia Vera. Of 8 patients with polycythemia vera 4 were markedly improved both clinically and hematologically; 1 was unimproved, 1 only slightly improved and 2 have just begun treatment. The remissions obtained have lasted as long as 6 months and may last longer. Two patients have begun to show hematologic relapse after 6 and 7 months, respectively. Improvement may begin within 2 weeks of treatment but full hematologic effect is rarely obtained until treatment for 2 or 3 months has been carried out. There have been no deaths in this group of patients.

Chronic Myelogenous Leukemia. One of the 5 patients treated with radio-active-phosphorus obtained an excellent remission which lasted several months. A second patient, now being treated seems to be responding satisfactorily. Three patients in late stages of the disease were unimproved by the drug. One of these died before

enough drug could be given, and a second has become radiation-fast due to considerable previous Roentgen therapy.

Chronic Lymphatic Leukemia. Two of the 4 patients with chronic lymphatic leukemia obtained good remissions. Here again it is too soon to tell how long the improvement will last. One of the latter has remained in excellent condition for almost a year. One very ill patient died shortly after being given the drug by mouth (coincidental death, P^{32} not responsible) and 1 patient has only recently begun to receive radio-phosphorus.

Acute Lymphatic Leukemia. None of the 4 patients with acute leukemia was benefited by radio-phosphorus.

Hodgkin's Disease. One of the 5 patients with Hodgkin's disease was considerably improved for a few months following the drug. This was a patient who was becoming Roentgen therapy-fast after 2 years of treatment. Four patients were not benefited by the drug. Of these, 3 had received previous Roentgen therapy. The fourth patient had a huge mediastinal mass that did not respond to P^{32} but did regress with sizable Roentgen exposures.

Lymphosarcoma. Two of the 6 patients with lymphosarcoma had good remissions following radio-phosphorus therapy. One of these had become Roentgen therapy-fast and has now been clinically improved for 6 months. Two patients were benefited for several months, with regression of subcutaneous masses, following which both suffered relapses. One patient, *in extremis* and anuric for days, improved and voided 7000 cc. following a single oral dose of 2.5 mc. of radio-phosphorus. The significance of this observation is uncertain, as the patient died of his disease shortly thereafter.

Multiple Myeloma. The 1 patient treated with radio-phosphorus was not benefited by the drug.

Reticuloendotheliosis. The 1 patient treated with radio-phosphorus improved remarkably. It is noteworthy that this patient had not responded satisfactorily to moderate Roentgen ray exposures.

Reticulum Cell Sarcoma. The 1 individual treated had previously received massive quantities of Roentgen rays and had become therapy-fast. He was not benefited by moderate doses of P^{32}.

Metastatic Carcinoma. Three patients, 2 with extensive gall-bladder carcinoma, and 1 with disseminated breast malignancy were not benefited by radio-phosphorus. The total amount of drug given these patients was probably not large enough to effect such radio-resistant neoplasms.

Summary and Conclusions. Administration of P^{32} has proven to be at least equal in value to older methods of radiation therapy in certain of the malignant blood dyscrasias.

In some respects it is superior: ease of administration, absence of marked radiation sickness, more concentrated effect on bone-

marrow with perhaps more prolonged remission in chronic leukemia and in polycythemia vera.

P^{32} has in our experience been of no value in the acute leukemias.

From the economic standpoint it is impossible to compare P^{32} with ordinary Roentgen ray therapy. Such comparison will have to await the end of the war when more of these great cyclotrons may be constructed and more material may become available. At present the supply is inadequate and the newly discovered metallurgic uses of the cyclotron and its products are threatening to eliminate its use for clinical medicine altogether for the duration of the war.

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THE INFLUENCE OF BLOOD TRANSFUSION AND INJECTIONS OF BURSA PASTORIS (SHEPHERD'S PURSE) EXTRACT ON THE CLOT RESISTANCE IN TWO HEMOPHILIACS

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In a previous communication[1] we described a new phenomenon regarding hemostasis which we called "clot resistance." Clot resistance was tested by applying a cuff pressure around the arm after bleeding had stopped from a finger-prick wound. This simple clinical procedure tests the ability of the clot, which has formed in the prick wound, to resist increases of pressure in the capillaries, arterioles and venules. We believe clot resistance is a measure of hemostasis, since one estimates both the solidity of the clot, and its ability to adhere to the skin wound.

In 55 normal subjects, 5 or more minutes following the cessation of bleeding from the prick wound a cuff pressure of 100 mm. of mercury for 3 minutes did not cause a renewal of blood flow. This was interpreted to mean that the clot which had formed inside of the prick wound was capable of withstanding cuff pressures up to 100 mm. Hg. In 2 cases of hemophilia, however, this pressure always dislodged the clot and renewed bleeding. Studies were done before and after blood transfusion and injections of *Bursa Pastoris*

* Aided in part by a grant from the Dazian Foundation for Medical Research.

extract in order to determine if such therapy would increase the clot resistance in the 2 hemophiliacs.

Methods. A constant temperature bath (37.5° C.) capable of heating 400 cc. of physiologic saline was constructed. The finger tip was cleaned with alcohol, and immersed for 2 minutes into the bath. The heated phalanx was removed temporarily while a prick wound was inflicted with an automatic lancet (blade dimensions: 0.5 x 2 x 6 mm.), after which the finger was immediately immersed into the bath. The distal area of the finger tip should be used, since injury to the periosteum or the bone is least likely. Bleeding times were accurately measured this way with a stop watch.[1,2] Cuff pressures of 40 to 100 mm. Hg were applied at various intervals after bleeding stopped. From 60 to 80 cc. of 2.5% sodium citrate solution were used with 500 cc. blood for transfusion. Doses of 3 cc. and 5 cc. of *Bursa Pastoris* extract* were given intramuscularly or intravenously. In these studies clot resistance tests were done by applying for 3 minutes 100 mm. Hg cuff pressure 5 and 15 minutes after bleeding had stopped. The systolic blood pressure should always be above the applied cuff pressure.[10]

TABLE 1.—THE EFFECT OF VARIOUS CUFF PRESSURES ON THE CLOT RESISTANCE IN 2 HEMOPHILIACS

Minutes after termination of bleeding time test	Case E. N. Mm. of Hg cuff pressure			Minutes after termination of bleeding time test	Case M. C. Mm. of Hg cuff pressure				
	0	40	100		0	40	60	80	100
1– 2	+			1– 3					+
2– 6	–			3–15		–			
6– 7	+			15–30	–				
7– 8	–			30–33					+
8– 9	+			33–34		–			
9–10	–			34–50	–				
10–14	+			50–62			–		
14–75	–			62–72				–	
75–81			+	72–75	–				
81–84		–		75–78					+
84–86	–			78–81		–			

+ bleeding; – no bleeding.

Results. Table 1 demonstrates a decreased clot resistance and abnormal bleeding from a finger-prick wound in 2 hemophiliacs. Case E. N. (colored, 18 years) showed a renewal of blood flow four times within 14 minutes without cuff pressure. Application of 100 mm. Hg cuff pressure 75 minutes after bleeding had stopped provoked a flow of blood from the prick wound. Lowering the cuff pressure from 100 to 40 mm. Hg was followed by a cessation of the flow within 30 seconds. In case M. C. (white, 24 years), no bleeding was observed without cuff pressure following the bleeding time test. Renewal of bleeding occurred three times following cuff pressures of 100 mm. Hg. Lowering the pressure to 40 mm. Hg caused the bleeding to stop within 7 to 20 seconds. In both cases pressures of 100 mm. Hg were necessary to dislodge the clot, since pressures of 40 to 80 mm. Hg did not renew bleeding.

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Even though the bleeding time was normal and arrest of hemorrhage occurred after the clot-resistance test, spontaneous bleeding took place in both cases subsequent to the bleeding tests after intervals of 1 and 3 days. Case E. N. developed bleeding from the prick wound on the second day and persisted to bleed for 2 days with hematoma formation. In case M. C., 3 days following the bleeding tests, a hematoma developed which involved the whole finger. On the 13th day the finger bled for 1 day from the prick wound. Nine months later the bleeding tests were repeated at which time 10 cc. of *Bursa Pastoris* extract were injected subcutaneously. No bleeding occurred afterwards.

Table 2 indicates that the other tests which were done in both patients were symptomatic for hemophilia, and that the blood pressure was normal.

TABLE 2.—ADDITIONAL DATA IN THE 2 HEMOPHILIA PATIENTS

Tests	Patient E. N.	Patient M. C.
Coagulation time (Howell)	40 min.	54 min.
Prothrombin time (Quick[12])	19 sec.	20 sec.
Bleeding time (Copley and Lalich[1,2])	182 sec.	168 sec.
Platelet count (Copley and Robb[3])	250,000	420,000
Syneresis (clot retraction)	Positive	Positive
Thixotropy[4] (reclotting phenomenon)	Positive	Positive
Blood pressure	114/75	120/80

TABLE 3.—THE INFLUENCE OF BLOOD TRANSFUSION AND BURSA PASTORIS EXTRACT ON THE CLOT RESISTANCE IN 2 HEMOPHILIACS

Patient	Date, 1942	Blood, cc.	*Bursa Pastoris* extract, cc.	Bleeding time, sec.	Coagulation time, min.	Clot resistance. Following bleeding time test cuff pressure applied after	
						5 min.	15 min.
E. N.	1–23			160	300	+	+
					300		
	1–23	500					
	1–24	500					
	1–24		6				
	1–25			105	7	–	–
					10		
E. N.	3–11			30		+	+
	3–11	500					
	3–12			205	226	+	+
					286		
	3–12		6				
	3–13		3				
	3–13			95	145	–	–
					320		
M. C.	3–14			105	30	+	+
					50		
	3–14	500					
	3–14			54	150	+	+
					150		
	3–15			80	65	+	+
					135		
	3–15		10				
	3–16			60	79	–	–
					79		
	3–16			130		–	+

+ bleeding; – no bleeding.

Table 3 shows results on clot resistance, bleeding time and coagulation time which were done 6 months or more after the initial findings shown in Table 1. The coagulation time in duplicate tests may vary from the same withdrawal. The shorter coagulation time was found, when the blood which entered the syringe first was mixed with tissue juice. Case E. N. was studied on 2 occasions; the first time while he suffered from a periapical abscess, and the second time when he complained of hemorrhages in the right arm. On the first occasion E. N. received two 500 cc. transfusions of citrated blood, and within the next 12 hours 6 cc. of *Bursa Pastoris* extract. No studies were done after the transfusions. However, 15 hours following the combined therapy of blood and *Bursa Pastoris* extract, the coagulation time was reduced to the normal range, and the clot resistance was increased. When this patient was studied again 6 weeks later, the clot resistance was found to be decreased. Coagulation studies were not done prior to transfusion; however, 18 hours following a 500 cc. transfusion, the coagulation time was still definitely prolonged and the clot resistance was decreased. This patient then received 9 cc. of *Bursa Pastoris* extract, and it was found that the coagulation time was not affected, but the clot resistance was increased. Case M. C. was studied when he entered the hospital complaining of hemorrhages in the right hip. Before transfusion, the coagulation time was 30 and 50 minutes and the clot resistance was decreased. Two tests were performed after the transfusion in intervals of 1 and 16 hours. In each instance the clot resistance was decreased, and the coagulation time was longer than it was before the transfusion. Ten cc. of *Bursa Pastoris* extract were injected. The bleeding time, coagulation time and clot resistance tests were repeated on the next day. The *Bursa Pastoris* extract again exerted no apparent influence on the coagulation time. However, the clot resistance in two successive tests was increased. In the second test 15 minutes after bleeding had stopped a minimal output of blood occurred. Usually the output of blood during positive tests was great in this patient.

Discussion. The results indicate that the firmness of the clot, or its ability to adhere to the wound, was abnormal in both cases of hemophilia. The clot resistance was found to be decreased on several different occasions in a period of time which lapsed over 6 months or more. The quality of the clot in hemophiliacs also explains recurrence of bleeding from the same wound which, although minor, continues to bleed until spontaneous arrest occurs, or persists until death ensues. The spontaneous recurrence of bleeding from the wound and into the finger suggests that movement of the arm or slight trauma to the finger dislodged the clot and renewed bleeding. This phenomenon was observed following the bleeding tests when nothing was given after the determinations. However, the phenomenon of spontaneous bleeding from the prick wound

never occurred when either the *Bursa Pastoris* extract alone, or combined with blood transfusion was given. Further, the effect of *Bursa Pastoris* extract upon the clot resistance in hemophiliacs is evident from our results. Whether this effect on the clot resistance is due solely to the extract of *Bursa Pastoris*, or the combined action of citrated blood and the former remains to be determined. We feel that the clot resistance test may also be of value in other hemorrhagic conditions.

In one instance, we found a normal coagulation time following the administration of blood and *Bursa Pastoris* extract. On two other occasions, however, neither the blood transfusion nor the injection of *Bursa Pastoris* extract appreciably shortened the coagulation time, whereas the clot resistance was increased. It has been shown by Johnson[9] that transfusions of 500 cc. of citrated blood will shorten the coagulation time within 30 minutes and that this effect may persist for 68 hours. We did not find this result from citrated blood in the two instances which we studied. In case E. N. there seemed to be no appreciable decrease of coagulation time; whereas in case M. C. a prolongation occurred 2 and 16 hours following the transfusion. This indicates that a shortening of the coagulation time following transfusions of 500 cc. of citrated blood may not necessarily occur. This is also true following the injections of 9 to 10 cc. of *Bursa Pastoris* extract.

Steinberg and Brown[14] who first made extracts from *Bursa Pastoris* and various other plants stated that the active hemostatic agent of the plant extracts was oxalic acid and that dicarboxylic acids when injected shorten the coagulation time. However, it will have to be established if the hemostatic action of *Bursa Pastoris* extract is due solely to dicarboxylic acids. It might well be that the hemostatic action of the plant extract is due to a phytothrombin,[5] a plant thrombin which is known to exist in papain[5,6] and which may be present in *Bursa Pastoris*. Previous to this study one of us (A. L. C.) searched the literature concerning *Capsella bursa-pastoris Medic. Cruciferæ* (Shepherd's Purse, Mother's Heart) and found that it is a plant which was well known and used as a hemostatic agent locally and internally several centuries ago.[7,11] Shepherd's Purse is one of the commonest weeds throughout North America and was introduced from Europe.[15] It was consumed in this country[8] and in China[13] as a vegetable. Therefore it cannot be very toxic. In view of this, the present findings with *Bursa Pastoris* extract and the use of Shepherd's Purse in former times as an internal hemostatic, it is possible that this plant or its extracts when taken orally may exert a hemostatic effect.

Summary. 1. A decreased clot resistance and abnormal bleeding from the finger wound was found in 2 hemophiliacs on several occasions over a period of 6 or more months.

2. The bleeding time which was measured previous to the clot resistance test was always within normal limits.

3. Injections of extract of *Bursa Pastoris* following blood transfusion increased the clot resistance in both hemophiliacs.

4. The coagulation time was found shortened on one occasion with the combined treatment of transfused blood and injected *Bursa Pastoris* extract, however in two other trials it was not affected significantly.

5. Apparently, no direct relationship exists between the coagulation time and the clot resistance.

6. The hemostatic effect of the plant *Bursa Pastoris* is discussed.

We wish to thank Dr. R. H. Major who made the hospitalization of both patients possible, Dr. M. Allen who in the course of this study suggested that we determine the effect of the plant extract upon the coagulation time, and both patients for their coöperation.

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THE SPINAL FLUID IN TUBERCULOUS MENINGITIS

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The spinal fluid in tuberculous meningitis is characteristically supposed to be clear, to be under increased pressure, to have a high cell count with lymphocytes predominating,[6] to show decreased sugar and chlorides, usually to contain increased globulin as determined by Pandy's or Noguchi's test, constantly to contain tubercle bacilli and an increased amount of protein and to give a Lange curve of approximately 0003334444.

According to Levinson,[3] different kinds of protein in the spinal fluid distinguish tuberculous from "suppurative" meningitis. He has advocated a chemical test to differentiate meningitis due to the

tubercle bacillus from other types of meningitis. In "suppurative" (non-tuberculous) meningitis sulphosalicylic acid gives a precipitate three times as great as mercuric chloride. In tuberculous meningitis the bichloride precipitate is supposed to exceed that of the sulphosalicylic acid.

Other authors[2] refer briefly to the possibility of the spinal fluid in tuberculous meningitis exhibiting predominantly neutrophilic cells. Others[5] admit the possibility of the spinal fluid cellular increase being neutrophilic, but only in those tuberculous meningitides complicated by some other infection. Few of the textbooks (Naegeli[8]) will grant with Sahli[11] that the spinal fluid in unmixed tuberculous meningitis may be cloudy* and contain an excess of neutrophils.

Merritt and Fremont-Smith[7] found no "frankly purulent" fluids in 84 patients with proved tuberculous meningitis. Most of the fluids were clear. A few had a ground-glass appearance. The neutrophil cells exceeded the mononuclears in 16 of 141 fluids. According to Purves-Stewart,[10] in an acute advancing tuberculous meningitis, 30% of the cells in the spinal fluid may be neutrophils. They may be present in the spinal fluid of patients with tuberculous meningitis according to Weschsler.[12] Oppenheim[9] found exceptions to Widal's dictum that tuberculous meningitis is characterized by the predominance of lymphocytes; purulent and cerebrospinal meningitis by neutrophils. Ford and Forsyth[1] hold tubercle bacilli are found in most spinal fluids of tuberculous meningitis.

Wilson and Bruce[13] state that there is a pleocytosis of 200 or more cells in the acute stages of tuberculous leptomeningitis. Neutrophils may predominate at the onset. They quote Birkel's finding of 8 turbid fluids in 189 specimens. They ascribe frankly purulent fluids to a secondary or mixed infection.

Having recently encountered 2 proved instances of unmixed tuberculosis of the meninges with cloudy spinal fluid and a pleocytosis of neutrophils in both cases, I investigated the spinal fluid findings in 111 other patients with tuberculous meningitis verified by autopsy or by finding tubercle bacilli in the spinal fluid. In 17 of these tuberculous meningitis was shown in each by isolating tubercle bacilli from the spinal fluid and also by autopsy.

In 35 cases the diagnosis was made from the presence of tubercle bacilli in the spinal fluid. In 66 the diagnosis was confirmed by autopsy only, by culturing tubercle bacilli from the spinal fluid on Herrold's medium[4] and later by autopsy. In 1 instance the tubercle bacilli were seen microscopically and cultured on Herrold's medium. In 5 cases the tubercle bacilli were seen and produced tuberculosis

* "Cloudy" is taken to be synonymous with turbid; the wire of the usual culture loop can barely be distinguished through a test tube of the fluid.

"Purulent" fluid is taken to be so turbulent and opaque that a culture loop cannot be seen through an ordinary test tube of it. The opacity is due to leukocytes (understood to be polymorphonuclear) and serum proteins.

in guinea pigs. In 3 instances a positive guinea pig inoculation was the only proof. In 1 patient tubercle bacilli were found only on guinea pig inoculation. This patient later showed tuberculous meningitis at autopsy. In all, autopsies were obtained in 76 instances. The records of 111 patients were obtained from the Cook County Hospital and the Presbyterian Hospital of Chicago. Two patients were in the West Suburban Hospital. These hospitals are general hospitals.

Analysis of Data. All of the patients died. In age they ranged from 6 weeks to 58 years. Patients aged 10 years or less were more than three times as numerous (58% of total number) as those over 30 years (18% of total number). There were 33% more males than females.

In 12 of the patients the fluid was cloudy and contained over 312 cells. In 4 of these cloudy spinal fluids the predominating cells were neutrophils. In 4 cloudy fluids the character of the cells was not studied.

Cells in the spinal fluid varied from 30 to 3000, 210 being the average number of cells in the spinal fluid. In 14 patients there were more than 100 cells in the spinal fluid. In 12 cases one-half or more of the cells were neutrophils. In 7 patients only neutrophils were seen in the spinal fluid. The course of the patients with neutrophilic pleocytosis did not differ in duration or severity from that of patients with the more usual preponderance of lymphocytes in the spinal fluid. The patients with spinal fluid cells predominantly neutrophilic were as frequently adults as infants.

The Pandy test was reported as positive in 112 of the 113 patients.

Total protein of the spinal fluid measured 20 to 712 mg. per 100 cc. It tended to parallel the degree of pleocytosis.

Two-thirds of the patients showed leukocyte counts in the peripheral blood of less than 10,000. Of the 65 instances with a differential count, 57 showed a predominance of neutrophils in the peripheral blood. This contrasts with Merritt and Fremont-Smith's[7] finding of a relative neutrophilia in only 16 cases of 141 studied.

In 5 of 16 patients Levinson's test gave incorrect results; denoting suppurative meningitis rather than the demonstrated tuberculous meningitis. In these cases the spinal fluid was clear to opalescent and there was no secondary infection.

Tubercle bacilli were found in 35 of the 81 patients whose spinal fluid was examined bacteriologically. Consequently in only 40% was this finding of value in bedside diagnosis.

Spinal fluid sugar was below 45 mg. per 100 cc. in the 25 patients with quantitative estimates.

The Mantoux test was negative in a boy of 13 years, a patient with tuberculous meningitis verified by autopsy.

Case Reports. CASE 1. Mrs. G., 28 years old, entered West Suburban Hospital in delirium under care of Dr. M. P. Palmer. She had vomited

and had headache for 2 days. Tuberculous lymph glands had been removed from her neck 2 months before. Roentgen rays of her chest were reported as negative.

Essential Findings. Temperature 103°, pulse 120 and respirations 30. Patient was thin but had good color. Irrational. Bilateral papilledema. No choroidal tubercles. Left eye lags on looking upward, otherwise no involvement of cranial nerves. Tuberculous laryngitis without hoarseness. Neck was stiff. Cervical lymph glands enlarged. Heart and lungs negative. Abdomen negative. Choreiform movements of right arm. Reflexes: those of the right arm less than on left, abdominal absent, right knee jerk sluggish, plantar normal. Blood leukocytes were 7200 per c.mm. Spinal fluid: cloudy, pressure 240 mm., total protein 850 mg., sugar 27 mg., 456 cells, 90% polymorphonuclear, Ross-Jones positive. Wassermann test negative; Lange 0012100000; no bacteria seen. Many cultures on various mediums yielded no growth. A guinea pig inoculated with the spinal fluid showed tuberculosis at autopsy.

The temperature climbed each afternoon to reach 106° on the sixth day of her illness, the day of her death.

Essential postmortem findings (Dr. E. Piette): chronic tuberculous laryngitis, recent miliary tuberculosis of both lungs, fibrous adhesive pleuritis, basilar meningitis, tuberculous in type.

Case 2. Mr. L., 28 years of age, entered the West Suburban Hospital in the care of Dr. K. M. Anderson. Three months ago while working long hours he had developed a severe "flu." Frequency and urgency followed. Pyuria was discovered. Three weeks ago he developed a progressively severe headache. Vomiting started 3 days ago.

He was muscular and well nourished. Temperature was 101°, pulse was 60 and respirations were 20. The pupils were equal and reacted normally. Papilledema was bilateral. No cervical adenopathy. The neck was stiff. Lungs were clear. Liver was just palpable. Spleen was not felt. External genitalia normal. Nodule felt in left lobe of prostate. Kernig's sign was positive. All deep reflexes reduced. Plantars normal.

The urine contained some pus. Blood leukocytes were 14,550; 88% neutrophils. The blood contained 53.5 mg. of urea, 4 mg. uric acid and 1.7 mg. of creatinine. Spinal fluid on admission: cloudy, under increased pressure, 785 cells, 80% neutrophils, Wassermann test negative, Pandy positive, many tubercle bacilli seen. Tubercle bacilli were also found in subsequent samples of spinal fluid. Repeated cultures of the spinal fluid yielded no other bacteria.

Roentgen ray showed miliary tuberculosis of the lungs.

Death occurred in the fifth week of his acute illness.

Table 1.—Spinal Fluid in 113 Cases of Tuberculous Meningitis

Age limits of patients	6 weeks to 58 years
Number under 10 years	66 (58%)
Number over 30 years	20 (18%)
Number with turbid or cloudy fluid	12 (10%)
Limits of cell count	30 to 3,000
Polys making 50% or more cells	12 (10%)
Polys only in	7 (6%)
Average number of cells	210
Number of cases with cells under 100	14 (10%)
Limits of total protein	20 to 712 mg.
Pandy positive in	112 of 113 tested (99%)
Leukocytes in blood below 10,000	39 of 59 cases counted
Levinson test	Negative 5 times in 16 cases so examined (31% error)
Tubercle bacilli found in	35 of 81 cases so examined (40%)

Summary. In tuberculous meningitis the spinal fluid may present all the gross and microscopic characteristics of "purulent" meningitis.

In 113 proved cases of this condition, the spinal fluid was cloudy in 10% and neutrophils constituted more than 50% of the cells in 10% of the cases.

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GASTRIC LAVAGE IN THE CONTROL OF TREATMENT OF PULMONARY TUBERCULOSIS*

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Although the presence of tubercle bacilli in the gastric contents was described in 1898,[11] gastric lavage as a diagnostic measure did not come into general use until the method was popularized by Armand-Delille only 15 years ago.[1,2] It was originally introduced as a method whereby positive bacteriologic evidence of tuberculosis could be secured in the case of children who seldom raise sputum, but it was quickly recognized that the method was equally applicable to adults who did not expectorate.[3,4,8,9,14] This represented a distinct advance, since it made a definite diagnosis possible in many previously doubtful cases.

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The reliability of gastric lavage as a diagnostic measure has been questioned on many grounds. Among these should be mentioned the possible presence of non-pathogenic acid-fast bacilli in the stomach contents, the possibility of contamination, and the relative value of direct smears, cultures and guinea-pig inoculations. In regard to the first question, Roper and Ordway,[14] reporting a series of 1000 patients, found 2 with positive gastric lavages in whom they could demonstrate no evidence of pulmonary or visceral tuberculosis. In our series of 180 adults with positive lavages, in 1 case we were unable to demonstrate any lesion, despite numerous roentgenograms, bronchoscopy and nasopharyngoscopy to rule out the nasopharyngeal ulcerations described by Trenis.[17] Subsequent lavages in this individual were negative. It must be recognized that when a proper technique is followed,[5] the incidence of false positives is negligible. A previous study made by one of the authors[19] has demonstrated the reliability of gastric lavage culture, and at the present time this method is used almost exclusively, although during the period covered by this report, culture and guinea-pig inoculations were done simultaneously on all specimens.

The question of the contagiousness of patients with a positive gastric lavage is frequently discussed. Ulmar and Ornstein[18] demonstrated that, in the absence of cough, bronchial secretions are brought to the pharynx by a mechanism of bronchial peristalsis, and are then swallowed. If these bronchial secretions contain tubercle bacilli, the gastric lavage will yield positive results. The immediate significance of a positive lavage, therefore, does not differ from that of a positive sputum, and implies the existence of an open tuberculosis in communication with the bronchial system. Since the bronchial secretions of these patients contain tubercle bacilli, they are at least potentially infectious, and become actually so during periods of upper respiratory infections, with coughing or sneezing.

The objection is frequently made that gastric lavage is too sensitive a test for widespread clinical application. It has been claimed that the lavage will remain positive long after the lesions have become clinically inactive, or that it is unreasonable to insist on complete bacteriologic negativity, as manifested by repeatedly negative gastric lavage cultures, in patients who have had far-advanced disease with extensive cavitation.[10] It has even been suggested that the lavage may be intermittently positive in such cases, even after effective collapse measures have been established. Since Stiehm[16] has shown that the percentage of positive lavages will increase the more frequently they are repeated, some observers apparently feel that, if they are done sufficiently often, even healed lesions might yield positive results. The purpose of this investigation is to determine the relationship between the stage of the disease, the institution of collapse therapy and the results of gastric

lavage. In our series, gastric lavages were done on each of 2 consecutive days. Each specimen was separately cultured and inoculated into a guinea-pig, and a negative report was given only when both specimens were negative to all tests.

Following collapse therapy, cough and expectoration are frequently abolished. It would logically follow that, if the efficacy of collapse therapy is to be judged by its ability to remove tubercle bacilli from the bronchial secretion, examination of the sputum would be particularly inadequate in this group of patients. Because of inability to cough, these patients either raise no sputum at all, or the material which they do raise comes only from the upper air passages. Examination of such material, with a report of a negative sputum, tends to give the physician a wholly unwarranted confidence in the clinical status of the patient. In this group, therefore, gastric lavage would be of particular value in determining the efficiency of the collapse. However, there are only a few scattered references[8,13,15] to the use of lavage for the control of collapse therapy.

To determine how long the lavage will remain positive after collapse has been established, the use of periodic gastric lavages as a routine measure in checking the clinical status of patients was introduced at Muirdale Sanatorium in March, 1939. During the 2 year period covered by this report, 491 adult patients were given a total of 1414 lavages at various stages during their treatment. Of this number, 180 patients (37%), at some time were found positive on lavage. These 180 positive lavages comprise the material on which this report is based.

TABLE 1.—DISTRIBUTION OF POSITIVE GASTRIC LAVAGES
Muirdale Sanatorium, March, 1939, to March, 1941

Group	Classification	Number	Total
O	No clinical evidence	1	1
I	Positive sputum and lavage	49	49
II	Sputum converted, lavage positive:		
	(*a*) Lavage converted	37	
	(*b*) Lavage still positive	28	65
III	Sputum negative, lavage positive:		
	(*a*) Lavage converted	20	
	(*b*) Lavage still positive	12	
	(*c*) Not repeated	21	53
IV	Sputum positive after lavage	12	12
		Total	180

To determine the clinical significance of the positive gastric lavages in these 180 patients, the results were divided into four main classifications (Table 1). In 1 case, as previously mentioned, no confirmatory evidence of tuberculosis was found. Group I consists of 49 cases in whom the positive lavages coincided with a positive sputum. In this group the sputum was usually negative on direct smear and concentrate. Lavages were done immediately, without

awaiting the results of sputum culture, which later proved to be positive. Although under these circumstances the lavage was merely confirmatory of the results of sputum examination, in many instances the bacilli were found in the lavage on smear, thus saving much time in establishing the diagnosis.

Group II consists of 65 patients who originally had positive sputa, but in whom the sputum subsequently became negative or absent. Despite the failure to find tubercle bacilli in the sputum, all were positive on gastric lavage. This group is of particular interest because it enables us to determine how long the gastric lavage can be expected to remain positive after the sputum has been converted. To determine this it was necessary to subdivide the group into: (*a*) those who became negative on lavage (37 patients), and (*b*) those in whom the last lavage was positive (28 patients). In Table 2 is shown the duration of positive lavages in this group. From the table it can be seen that, while in a few cases the lavage culture will be negative in less than 6 months, in the majority of cases from 12 to 18 months is required. In 1 case, with a bronchopleural fistula and tuberculous empyema, the lavage is still positive 5 years after the sputum became negative. Of the 37 patients whose lavages were converted while under observation, 62% were negative 18 months after sputum conversion, and 90% were negative within 2 years. This is an important consideration when the use of lavage for the control of collapse therapy is discussed, since, if negative lavage cultures are required before patients are discharged or permitted to take ambulatory pneumothorax, the period of sanatorium residence will be considerably prolonged.

TABLE 2.—DURATION OF POSITIVE LAVAGE AFTER SPUTUM CONVERSION

Months	Lavage converted after	Lavage positive after
0– 3	0	0
3– 6	3	2
6– 9	3	8
9–12	8 (40%)	8
12–18	9 (62%)	3
18–24	9 (90%)	3
24–	5	4
	37	28

Group III consists of 53 patients who never were positive on sputum examination, but in whom tubercle bacilli were discovered on lavage. In this group the lavage furnished the only positive bacteriologic evidence of tuberculosis. In 21 of these cases, the lavage was not repeated because the patients refused further lavage, left the institution or died. The remaining 32 cases were again subdivided, as in Group II, into: (*a*) those in whom the lavage was converted (20 patients), and (*b*) those in whom the lavages are still positive (12 patients). From Table 3 it can be seen that, in the

group with negative lavages, 75% were negative within 12 months and 95% within 18 months, as compared with 40% and 62% in Group II. As a rule, therefore, patients who have never had a positive sputum will completely heal their tuberculosis in an average of 6 months less than those who have been sputum-positive. This is to be expected, since it is merely a reflection of the fact that the gastric lavage will become positive earlier than the sputum, and thus permits diagnosis in a less advanced stage.

TABLE 3.—DURATION OF POSITIVE GASTRIC LAVAGE

Months	Lavage converted after	Lavage positive after
0– 3	1	2
3– 6	6	0
6– 9	4	2
9–12	4	1
12–18	4	3
18–24	0	2
24–	1	2
	20	12

This is well illustrated by the results in Group IV, 12 patients originally positive on lavage alone in whom the sputum subsequently became positive. This is an unfavorable sequence of events, indicating progression of the disease. Of the 12 patients in this group, 3 are dead and 4 have shown marked extension of their lesions.

In discussing the relationship of gastric lavage to collapse therapy, it was pointed out that, while negative gastric lavages prior to discharge were theoretically desirable, the prolongation of sanatorium care might be economically impractical, and the improvement in results might not warrant the additional expense. To obtain evidence on this point, a detailed study was made of the 57 cases in Groups II and III, who eventually became negative on lavage, to determine the exact relationship between the institution of an apparently effective collapse and lavage negativity. It was felt that in many instances the persistence of a positive gastric lavage might mean not so much a delay in healing time, as the necessity for supplementary measures, such as pneumonolysis, to render the collapse effective.

Of the 57 cases (Table 4), 7 were not given any form of collapse therapy. Of the remaining 50, 14 received phrenic paralyses, 24 were given pneumothorax, and 12 were subjected to major surgery, including thoracoplasty, extrapleural pneumothorax and paraffin pneumonolysis. In the entire group there were 16 minimal, 15 moderately advanced and 26 far advanced cases.

Of the 14 cases treated by phrenic nerve paralysis, 11 were minimal and 3 moderately advanced. The interval between the phrenic nerve interruption and negative gastric cultures varied from 2 to

25 months (Table 5), averaging 8 months for the entire group. In 11 of the 14 cases, negative lavages were obtained in less than 9 months. Of the remaining 3, 1 had not been lavaged for the preceding 7 months, and the other 2, both minimal cases with fibroid apical lesions remained positive for 25 months. If these 2 are excluded, the average for the entire group is only 6 months.

TABLE 4.—CLASSIFICATION AND TREATMENT IN CONVERTED LAVAGES
(Groups II and III (*a*), 57 Cases)

Treatment	Minimal	Moderate	Far	Total	Average interval
Routine	3	3	1	7	?
Phrenic	11	3	..	14	6 mos.[1]
Pneumo.	1	9	14	24	10 mos.[2]
Surgical	1	..	11	12	9 mos.
	16	15	26	57	

[1] Excluding 2 cases, each 25 months.
[2] Excluding 4 cases, 27, 29, 37, 45 months.

TABLE 5.—INTERVAL BETWEEN EFFECTIVE COLLAPSE AND NEGATIVE LAVAGES
(50 CASES)

Months	Phrenic	Pneumo.	Surgery	Total	%
0– 6	7	8	5	20	
6–12	4 (80%)	6 (60%)	3 (66%)	13	66
12–18	1	2	3	6	80
18–24	..	4 (90%)	1	5	86
24–	2	4	..	6	
Total	14	24	12	50	

The pneumothorax group consisted of 1 minimal, 9 moderately and 14 far-advanced cases. Many of these had bilateral lesions, which in some instances, made evaluation of the effectiveness of unilateral collapse difficult. When supplementary measures, such as pneumonolysis, were necessary to convert an ineffective pneumothorax into an effective collapse, the interval between the establishment of effective collapse and lavage negativity was determined, and was found to range from 1 month to 45 months. Of this group, 60% were negative in less than 1 year, and 90%, or all but 4, were negative within 2 years. In every one of these 4, far-advanced bilateral disease was present. If these 4 are eliminated, the average interval for the remainder of the group was 10 months.

With the exception of 1 minimal case, in which a paraffin pneumonolysis was done, all of the patients submitted to major surgery had far-advanced disease. Despite this fact, the interval from completion of the surgery to negative lavage cultures ranged from 1 to 22 months, averaging 9 months. This interval, which is less than that for patients treated by pneumothorax, shows the great effectiveness of surgical collapse of advanced disease, and is in sharp opposition to the prevalent opinion that, in such cases, a requirement of negative lavage cultures prior to discharge is unreasonably strict.

Table 5 summarizes the results in the entire group of 50 patients treated by collapse therapy in whom the gastric lavage was converted; 66% were negative in 1 year, 80% in 18 months and 86% within 2 years (in a group of patients consisting of 26% minimal, 24% moderately advanced, and 50% far-advanced cases). These results indicate that the gastric lavage tends to remain positive until adequate collapse has been established, and thereafter becomes negative when sufficient time has elapsed to allow complete healing. Far from being too sensitive, it is the nost reliable laboratory evidence we have of the clinical status of the individual patient. It is more reliable than the sputum examination, and particularly in the group treated by collapse therapy, is an indispensable measure in evaluating the results.

Summary. 1. In a group of 491 adult patients with tuberculosis, a total of 1414 gastric lavages was done. Of this number, 180 patients (37%) were positive on at least one examination.

2. An analysis of these 180 patients with positive gastric lavages is presented.

3. The duration of a positive lavage after the sputum has become negative was determined in 57 cases. In 90% of this group, the lavage cultures and guinea-pig inoculations were negative in less than 2 years, and averaged 11 months for the entire group.

4. In a group of 50 patients treated by collapse therapy, 86% were negative to gastric lavage culture and guinea-pig inoculation in less than 2 years, with an average interval of 8.5 months.

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SUCCESSFUL REMOVAL OF HEMANGIOMA OF THE LUNG FOLLOWED BY THE DISAPPEARANCE OF POLYCYTHEMIA

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The rarity of hemangioma of the lung may be judged from the fact that no previous case has been encountered by the pathologic department of this hospital. It is not surprising, therefore, that a search of the literature has yielded very few reports describing the occurrence of such a lesion. This has led us to report the following case in which the diagnosis was made on the basis of clinical and laboratory findings and which is, so far as we are aware, the first reported case in which a cure was brought about by pneumonectomy.

Cavernous hemangioma of the lung is not mentioned in Henke and Lubarsch's Handbook of Pathology.[6] This work, however, does refer to a case described by de Lange and de Vries-Robles[2] (1923) of an infant aged 2½ months, whose lungs, at autopsy, were seen to contain 2 small tumors, which microscopically were shown to be capillary hemangiomas. Wollstein[9] in 1931 reported a malignant hemangioma of the lung which was found at autopsy in a child aged 4 months, and Hall,[5] in 1935, also described a malignant pulmonary hemangioma in a woman aged 40. In both these malignant cases there was a distinct anemia and an appreciable lowering of the red blood count. Bowers,[1] in 1936, reported the death of a new-born child, caused by hemorrhage from a ruptured pulmonary hemangioma. In 1939, Duvoir *et al.*[3] related the case of a child who, from 1932, had been subject to paroxysms of dyspnea and who had congenital lues. Roentgen ray films of the chest showed an opacity which was thought to be caused by a lipoma. Pathologic examination of the removed tumor, however, showed the mass in the lung to be a hemangioma. The child died of pneumonia 5 years later and autopsy revealed many lipomata, visceral angiomata and 1 lipoangioma. Cyanosis and clubbing of the fingers were not mentioned and no blood examination was recorded.

Rodes,[7] in 1938, described a case of hemangioma in which there was a polycythemia and stated that he could find no previous record of polycythemia arising from such a cause. This patient had been cyanosed and dyspneic for as long as he could remember. Clubbing of the fingers was noted when he was 15, and clubbing of the toes appeared 8 years later. In 1935, when he was 25, the cyanosis and dyspnea were more marked and hemangiomata appeared on his lips. His heart was normal in size and shape and

showed no evidence of congenital defects; the spleen was not palpable. The hemoglobin varied from 108 to 118%, and the red blood cell count was 7.2 to 7.5 million cells per cmm. In May, 1936, he had a sudden hemoptysis and died 6 days later from repeated bleeding from the lung. Autopsy showed 2 hemangiomata in the right and 1 in the left lung.

In November, 1939, Smith and Horton[8] reported the case of a man, aged 47, with polycythemia associated with an arteriovenous fistula in the lung. This patient had been a "blue" baby, and cyanosis and clubbing of the fingers had been noted by an Army physician when he was 23 and were observed again 17 years later at the Mayo Clinic. The spleen was not palpable and the patient showed no evidence of congenital heart disease. His hemoglobin was 20.6 gm. per 100 cc.; the red blood count varied from 5,440,000 to 6,220,000 per cmm.; the total blood volume was increased (figures not given). At that time the patient was thought to have atypical polycythemia rubra vera and was treated by phenylhydrazine and venesection. In 1938, after many venesections and having taken a considerable amount of phenylhydrazine, his condition was relatively unchanged. The cyanosis and clubbing were still marked. The blood findings—red blood count 6,470,000, hemoglobin 23.7 gm. per 100 cc., and blood volume 121 cc. per kg.—were even more characteristic of polycythemia vera. At this time, however, a continuous bruit was heard in the region of the base of the right lung. Roentgen ray examination of the chest showed some infiltration of the lung in this area, which at first was thought to be bronchiectatic. However, Roentgen ray films after the injection of a radiopaque medium into the basilic vein showed two dilated vessels arising in the right hilum and communicating in the parenchyma of the right lung where the bruit was heard. The final diagnosis was arteriovenous fistula of the right lung.

Case Report. Mrs. J. S., aged 23, was admitted to this hospital for the second time in January, 1940, complaining of an attack of dizziness, faintness and thick speech. The patient had never been robust and, in 1932, at the age of 15, had been put to bed with the diagnosis of "a leaking valve." Clubbing of the fingers was first noted at that time. Following this she became aware of shortness of breath on climbing one flight of stairs. In 1937, on the occasion of a pelvic operation, her hemoglobin was found to be 91% (14.2 gm. %) and the red blood count 6.3 million per cmm. In 1938, because of chest symptoms, she was sent to the Muskoka Hospital for Tuberculosis where clubbing of her fingers was again noticed and, in addition, cyanosis was observed. The hemoglobin at that time was reported to be only 78% (12.2 gm. %). Roentgen ray examination of the lungs revealed an infiltrating process in the right middle and lower lobes which was shown by lipiodol injection not to be bronchiectatic. The patient was transferred to this hospital in May, 1938, with the following statement from Dr. C. B. Ross of the Muskoka Hospital: "The lung condition is either a fibrosis giving a rather unusual clinical picture or something in the nature of a vascular endothelioma." On this, her first admission to this hospital, slight generalized cyanosis, clubbing of the fingers, and some

suppression of the breath sounds medial to the vertebral border of the right scapula were noted. Her heart was not enlarged and presented no murmurs. The spleen was not palpable. The hemoglobin was 95% (14.8 gm. %); the red blood count 4.7 million per cmm. The patient did not wish to submit to bronchoscopic examination and so left hospital without further investigation, the provisional diagnosis being pulmonary fibrosis.

During the next 18 months she became more dyspneic, more cyanosed and more easily tired. In January, 1940, she was seen by one of us because of an attack of dizziness, faintness and thick speech—symptoms similar to those described by Smith and Horton[8]—and she was readmitted to this hospital.

On this second admission, in addition to the rather marked cyanosis and clubbing of the fingers, there was some diminution of movement and of lung resonance in the right scapular region but no bruit was heard. The heart was not enlarged and there were no cardiac murmurs. The spleen could not be felt. Blood examination showed a marked polycythemia, the hemoglobin being 140 to 146% (21.8 to 22.8 gm. per 100 cc.), and the red blood count 9 to 9.6 million per cmm. The packed cell volume was 80%. The total blood volume was raised to 8500 cc. (normal is 3500 cc.). The vital capacity was 1700 cc. Fluoroscopic and Roentgen ray examinations demonstrated a shadow in the right middle and lower lobes, similar to that previously noted at the Muskoka Hospital.

It was felt that the cyanosis which the patient exhibited was not secondary to the polycythemia since it had been present before any increase in red cells or hemoglobin had occurred and was central rather than peripheral in origin. That this was true was shown: first, by the observation that when the patient's hand was immersed for 10 minutes in a water bath at 45° to 47° C. it became uniformly and more deeply cyanosed; and second, by the fact that arterial blood, obtained from the femoral artery and also from the veins of the heated hand by the method of Goldschmidt and Light,[4] was only 70 to 75% saturated with oxygen (normal saturation is 95%).

The possible causes for such an arterial oxygen unsaturation were: (1) a congenital heart lesion; (2) a generalized pulmonary condition, such as Ayerza's disease, in which none of the blood leaving the lungs is properly aerated; (3) a local lung condition allowing by some means, such as a shunt, the passage of a proportion of blood directly from pulmonary artery to pulmonary vein. As this patient presented no evidence of congenital heart disease and no suggestion of any generalized pulmonary disease, and as she did show a circumscribed local lesion in the lung on Roentgen ray examination, it was felt that she probably had an abnormal arteriovenous communication in the lung in the nature of a cavernous hemangioma. The cyanosis could then be adequately accounted for and the other signs and symptoms (dyspnea, dizziness, fatigue, polycythemia and clubbing of the fingers) could be considered as secondary manifestations of the resultant anoxemia.

An attempt was made by artificial pneumothorax to close this arteriovenous communication in the lung but, although a good collapse was obtained, no change could be noted in the degree of cyanosis and no increase occurred in arterial oxygen saturation (Table 1). Pneumonectomy was then performed by Dr. N. Shenstone and Dr. R. Janes on February 14, 1940. The details of this operation will be reported by them elsewhere.

At operation, when the right lung root was clamped it was found that the cyanosis disappeared promptly. The exposed lung showed a cyanosed mass occupying the upper part of the right lower lobe. This was removed along with the whole of the right lung. The patient was very uncomfortable for a few days but within a week she was sitting up in bed, all signs of cyanosis having disappeared and her complexion now a rosy pink.

Examination of her arterial blood at this time showed it to be normally saturated with oxygen (Table 1). Prompt disappearance of polycythemia was accounted for, at least in part, by the occurrence of a large hemothorax and by the loss of blood at operation. The patient was allowed out of bed at the end of 6 weeks and was discharged from hospital 2 months after her operation.

TABLE 1.—BLOOD FINDINGS

Date, 1940	Hemoglobin, %	R.B.C., m. per c.mm.	Arterial blood: O_2 content, vol. %	Arterial blood: O_2 capacity, vol. %	Arterial blood: Saturation, %
21/1	140	9.4	21.6	29.6	73.0
23/1	138	9.0	22.3	29.9	74.5
After Pneumothorax					
6/2	135	8.3	21.3	29.6	72.0
After Pneumonectomy (Feb. 14, 1940)					
23/2	93	5.4	18.4	19.3	95.3
17/4	73	4.4			
1941					
25/4	71	4.3			

The pathologist's report on the lung removed at operation reads, in part: "Involving the mid-portion of the lower lobe is a large angiomatous mass, roughly measuring 8 x 6 x 4 cm., made up of cavernous sinuses linked up with one another. Some of the caverns measured up to 1.5 cm. in diameter. The lining of these sacs was smooth and greyish-white in color. On sewing up the cut surface of the lung and injecting one of the branches of the pulmonary artery this angiomatous mass was distended." The pathologic diagnosis was "cavernous angioma of the lung."

Ten days after discharge the patient was feeling well and exhibited no sign of cyanosis. The clubbing of her fingers was less marked and a long-standing acne-like eruption on her face had vanished. She was less tired and her exercise tolerance had greatly increased. In September, 1940, 7 months after operation, she showed further improvement both subjectively and objectively. In March, 1941, she reported that, although 6 months pregnant, she was more fit than she had ever been, that there was no return of the cyanosis, and that all clubbing had disappeared except from one thumb. By the end of April, 1941, all the clubbing had entirely disappeared, she was looking and feeling well, the pregnancy was progressing normally, and the only abnormality found on blood examination was a mild degree of secondary anemia.

Summary. The case reported is one of cavernous hemangioma of the lung. This pathologic defect allowed the flow of a considerable volume of unoxygenated blood directly from the venous to the arterial circulation which resulted in a marked cyanosis of central origin with secondary manifestations of clubbing of the fingers and a true secondary polycythemia. When the patient was seen by us in January, 1940, diagnosis was relatively easy: polycythemia, cyanosis not due to peripheral stagnation, absence of signs of congenital heart disease, and an infiltrating lesion of the lung could only be accounted for by such a lesion. Great credit is due to Dr. C. B. Ross of the Muskoka Hospital for suggesting the diagnosis of vascular endothelioma of the lung before the development of polycythemia.

Removal of the hemangiomatous pulmonary growth was accomplished without any particular difficulty by the surgical division. This was followed by an immediate cessation of cyanosis, by a rapid decrease in the polycythemia, by a more gradual disappearance of clubbing of the fingers and, after a short period, by a definite increase in general health and sense of well-being.

We wish to thank Professor Duncan Graham for permission to report this case.

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SINGLE COMBINED TREATMENT FOR GONORRHEA

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The value of the sulfonamides in treatment of gonorrheal urethritis is well established. However, cure rate has not reached 100% regardless of the derivative of the drug used. The percentage of cases which have failed is from 10 to 40%, according to the drug employed and the method used. These cases which underwent an intensive course of sulfonamide and failed have been treated in many ways, such as repeated courses of sulfonamides, irrigations, typhoid vaccines, gonococcus vaccine and fever therapy.

Fever therapy in the treatment of active gonorrheal urethritis was initiated by the Kettering Institute for Medical Research. Carpenter, Boak, and Warren[7] found the rationale of such therapy in working out the thermal death time of various strains of gonococcus. The lethal temperature ranged around 106° F. for a duration of 6 to 24 hours. Several investigators compiled statistics in the use of fever therapy alone for treatment of gonorrhea.

With the advent of sulfanilamide, physicians began to combine this drug with fever therapy. Ballenger and Elder,[1] for instance, using ordinary dosages of sulfanilamide and 3 fever sessions averaging 4 hours on alternate days at temperatures up to 104° F., claimed

that 100% of the cases were cured. Later (1939) they reported a cure rate of 90% on a larger series of cases. Owens, Wright and Lewis[5] administered sulfanilamide for 4 days followed by 10 hours of 106° F. and reported almost 100% of them as being cured. Belt and Falkenberg,[2] using sulfanilamide for 7 days, 5 hours of fever therapy at 106° F. on the 3d, 5th and 7th days, reported 86% of 49 cases as being cured. Kendall, Simpson and Rose[6] claimed 100% results in 31 cases, using the combination of sulfanilamide and fever.

In an endeavor to improve the treatment of gonorrhea by speeding recovery, we carried out the following clinical study. The plan was to develop a high concentration of sulfathiazole in the patient, then subject him to hyperpyrexia. If one such treatment would prove effective, time can be saved for the patient and the public health problem simplified.

Selection of Cases. Our cases are all seamen with an age range of from 19 to 47 years who have picked up various gonococcal strains from many countries bordering on the sea. The number of previous infections per patient varied from 0 to 5. The duration of infection was from 1 to 60 days. Most of the cases were uncomplicated. The few that had acute gonorrheal epididymitis are so listed.

All the patients on entry to the hospital were given a physical examination and a history was taken. Smears and cultures were taken to confirm the diagnosis.

Procedure. The patient is given 1 gm. of sulfathiazole starting at 2 P.M. the day before the fever therapy and continued every 4 hours until a total of 5 gm. are administered. The man is then given an enema and, following this, a hot tub bath which brings the surface temperature to about 102° F. The patient is then put into a preheated fever cabinet and his temperature slowly raised until 106° F., by rectum, is reached. This takes about 1 hour. This temperature is maintained for about 7 hours. During his stay in the hypotherm cabinet the patient is given, by mouth, from 3 to 4 liters of normal saline, flavored with Karo syrup. Following this treatment the patient is warmly wrapped in blankets, brought to his room and given fruit juices and milk for the next 24 hours.

Criteria of Cure. The criteria of cure included complete cessation of all objective symptoms, disappearance of discharge and dysuria and clear urine in the 2 glass test. Bacteriologic and cultural examinations were done on all patients in the following manner: Starting on the 2d day after fever therapy and on subsequent 2d or 3d days thereafter for 3 times, the patient was sounded, his urethra massaged gently against the sound and the sound removed. A prostatic massage was next done for microscopic and cultural examinations of strippings. Three consecutive negative cultures were required before the patient was discharged.

Data. Table 1 shows the results of the combined therapy given to the uncomplicated cases of gonorrhea.

TABLE 1.—RESULTS OF COMBINED THERAPY IN UNCOMPLICATED CASES

Previous treatment	No. of combined treatments	Patients	Cures	Failures	% cures
None*	1	25	22	3	88
Sulfathiazole (20 gm.),† 8 days	1	20	18	2	90
One course of sulfonamide† plus sulfathiazole (20 gm.), 8 days	1	26	22	4	85
One course of sulfonamide† plus sulfathiazole (20 gm.), 8 days	2	4	2	2	50
Total	..	75	64	11	85.3

* Duration of disease of those cured, 3 to 30 days; those who failed, 5 to 8 days.
† Period of rest between treatments, 3 to 10 days.

Two cases of acute gonorrhea accompanied by epididymitis were given one course of sulfathiazole and failed to respond. These patients then received the combined treatment which resulted in a cure of each.

Comment. We have found several interesting factors in our study. It would appear that duration of illness has no bearing on the efficiency of the combined sulfathiazole and fever therapy. Success has been obtained in cases with a duration of as short as 3 days.

In this series, the combined therapy of sulfathiazole and hyperpyrexia successfully cured 85.3% cases of gonorrheal urethritis. Necessity of a rapid cure is the chief indication. It is of distinct advantage when previous treatment has failed.

The treatment should be confined to the young and vigorous, as it is drastic. The most annoying complications are herpes about the face as a result of the heat. Some patients suffer malaise and weakness for 2 to 3 days. A disadvantage is the expense, as a nurse's constant attention is required as well as relatively expensive apparatus. Large doses of the sulfonamides are not without risk and harm as we have cautioned in previous publications.[3] We recently had one patient develop anuria from 300 gr. of sulfanilamide, given at a rate of 80 gr. per day. No calculus or mechanical block was involved. He was anuric for 8 days, then recovered. French[4] has called attention to an interstitial myocarditis that may result from these drugs.

Conclusion. Of 75 cases of uncomplicated previously untreated gonorrheal urethritis, treated with sulfathiazole 5 gm. for 18 hours prior to fever therapy of 7 hours of 106° F., 88% were cured (22 of 25). Of those receiving this therapy after one course of sulfonamide, 90% were cured (18 out of 20). Of those receiving this therapy after more than one course of sulfonamide, 85% were cured (22 of 26). Of 2 cases of epididymitis not included in this list, both recovered after one treatment of the combined therapy.

The chief indication for this type of therapy is the necessity of a rapid cure for selected patients.

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BLOOD PRESSURE AND SULFOCYANATES (THIOCYANATE)

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Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substances. Although for many years nitrites have been the depressor substances of choice in the treatment of hypertension, the natural blood concentration of sulfocyanates is approximately 50,000 times that of nitrites.

In our studies, the natural concentration of blood sulfocyanates in 241 persons to whom the drug had never been administered ranged from 0.31 to 2.55 mg. per 100 cc. of blood. In the groups of individuals whose pressure was in the normal range, the blood sulfocyanate concentration averaged 1.2 mg. per 100 cc. of blood.[4]

Each individual has a fixed natural blood concentration of sulfocyanates that does not change appreciably from week to week. Of 29 unselected persons who had never taken sulfocyanates, picked at random without regard to blood pressure or other factors, the initial blood concentrations ranged from 0.36 to 2.04 mg. per 100 cc. of blood. Repeat determinations, made from 1 to 2 weeks later, showed no variation in 3; variation of 0.10 mg. or less in 15, and a mean variation for the 29 of 0.14 mg. per 100 cc. of blood.[4]

The constancy of the blood concentration of sulfocyanates is quite marked not only in the subjects we have studied, but also in patients to whom sulfocyanate has been administered for therapeutic effects. While different individuals vary greatly in their reaction to the

drug, each person tends to show a very constant level after becoming adjusted to the influence of the drug.

Studies of 241 individuals who had never received sulfocyanate therapy indicate that blood pressure varies in inverse ratio to the blood sulfocyanate concentration.[4]

For analytical purposes in this work, we have classified blood pressure readings as follows:

Below 106 systolic: hypotension
106 to 130 systolic: normal pressure
131 to 140 systolic: borderline
141 and above systolic: hypertension.

Diastolic pressures have been classified similarly, diastolic readings being expected to be approximately two-thirds of the above readings. These figures are in keeping with the published work of the Association of Life Insurance Medical Directors and The Actuarial Society of America, which places 128 mm. as the maximum normal systolic pressure and 84 mm. the maximum normal diastolic pressure.[2]

The averages of blood sulfocyanate concentrations for each blood pressure group make definite curves for systolic and diastolic pressures. Also, all cases presenting high blood pressure fall in the low sulfocyanate concentration group; while in the high blood sulfocyanate group, no hypertension cases appear. Above a blood concentration of 1.54 mg. no diastolic pressures above 90 mm. were found, and the only systolic pressures above 130 mm. were one of 150 mm. and one of 138 mm.

All of our studies have been made on blood serum. Barker and others have made exhaustive studies of the sulfocyanate content of various body tissues and fluids. Sulfocyanates are present in all parts of the body, though some tissues contain much more than others.

Many vertebrates are known to have sulfocyanates present in considerable amounts throughout their bodies; no vertebrates are known to be without it.

Blood Pressure Studies. As described in earlier reports of this work[1,3] every effort has been exerted to assure results that would not be influenced by variations in diet, exercise or other factors. Accordingly, every person admitted to the State Prison and to the State Hospital for the Insane was studied. Samples of blood were collected on the second morning after admission before breakfast and before tobacco was used. All subjects were at rest in the institutions for observation and general study and appraisal. There was reasonable similarity of diet for all individuals in both institutions. Apparently we had as exact a control over the environment, diet and activities of the subjects as was possible. Studies were made of 241 consecutive admissions.

To secure maximum accuracy in the study, all determinations were made by a graduate student in chemistry, using an Evelyn

photoelectric colorimeter.[4,6,7,8] Tests showed that a filter of wave length 440μ was correct for this work. Blood serum was used for the tests. As a further check on accuracy, recovery tests by silver nitrate precipitation were made and indicated that the results were well within the acceptable limits of technical error.

Similar studies on a large number of other persons in private life have been made. These show the same very definite inverse ratio of blood sulfocyanate concentration to blood pressure. However, since they were not under such strictly controlled environment, they have not been included in our statistics (Chart 1).

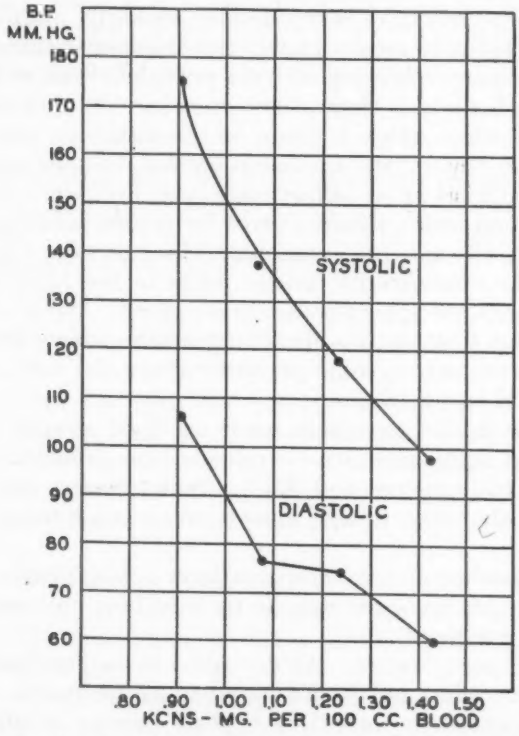

CHART 1.—Results of sulfocyanate studies on prisoners at the State Prison. This shows the inverse ratio between blood sulfocyanate concentration and blood pressure levels.

Pressor Substances. In the human body there appears to be a delicate balance of control over blood pressure. There is a pressor substance that is associated in some way with the adrenals and perhaps also with the kidneys. The normal tonicity of the arteriolar musculature is maintained by elastic tissue and the action of the pressor substance on the muscular coat. In Addison's disease there is a deficiency of this pressor substance and blood pressure is low. Undoubtedly, epinephrine plays a very important rôle in the

maintenance of tone in the vessel walls whether low, normal, or high pressure exists, and epinephrine has been generally accepted as the essential pressor substance. Occasionally a tumor of the adrenal gland is seen, such as the paraganglioma, in which severe rises in blood pressure occur but may be relieved by removal of the tumor or the adrenal.[9,11,13]

In some cases of hypertension there appears to be an excess of pressor substance. There are also depressor substances in the body which help to counterbalance the effects of the pressor substance. Nitrites, present naturally in minute amounts,[10] have been used as depressor substances for many years. Sulfocyanates are the only known depressor substances present naturally in the body in appreciable amounts and they exert very satisfactory depressor effects on blood pressure at any level. Our work has shown that low blood pressure is likely to be associated with a high blood sulfocyanate concentration, that high pressure is associated with a low blood sulfocyanate concentration, and that normal and borderline pressure cases occupy intermediate positions. It is especially noteworthy that higher concentrations of sulfocyanates are not associated with hypertension.

Blood Pressure Control. The whole story of blood pressure control cannot be found in either pressor substances or sulfocyanates alone. There is a delicate balance of control between the two substances and either may be present in the body in excess, in normal amounts, or be deficient; and any combination of these states is also possible. This is well illustrated by the fact that in many patients hypertension may be corrected without raising the blood sulfocyanate concentration above normal natural levels, while other cases require that they be stabilized at a high concentration; *i. e.*, enough sulfocyanate must be kept in the blood stream to counterbalance an excess of pressor substances.

Sulfocyanates appear to act efficiently in the reduction of blood pressure of any level, whether the pressure be high, low, normal or borderline. Unless too much change in the arterioles and capillaries has occurred there appears to be very little restriction on the degree of reduction that is possible.

The usual approach in the treatment of hypertension is on the plane of control of symptoms; only relatively rarely is one able to discover basic causes for the condition. Relief of symptoms is of definite value to the patient but unless the pressure is lowered there can be only symptomatic relief.

The control of blood pressure is further complicated by other etiologic factors. We attempt to eliminate all cases that represent a physiologic rise in blood pressure due to emotion or exercise and in which the rise in blood pressure is the result of increased cardiac output; such rises are transient and we do not classify them as hypertension. The sustained elevations of pressure resulting from

increased peripheral resistance to the blood flow represent pathologic hypertension and it is with this type of cases that we have been working.

Many substances will reduce systolic blood pressure temporarily. Most of this relief is psychic in nature. The attitude and manner of the attending physician may raise or lower pressures. Pressures may rise 50 points or more in patients with hypertension due to careless remarks by the physician. But unless drugs lower the diastolic pressure as well as the systolic pressure, there is little or no benefit for the patient.

Nitrites are typical of the large group of drugs that lower systolic pressure temporarily; but the diastolic pressure is not lowered satisfactorily and systolic improvement is not likely to persist very long. A satisfactory depressor substance must relieve spasm of the arterioles, thereby lowering the diastolic pressure. After hypertension has persisted for a long time and arteriolar spasm has been replaced by arteriolar sclerosis with calcification, relaxation is no longer possible and it is doubtful if any treatment other than symptomatic is feasible.

Treatment. This raises the point as to the proper time at which to institute treatment for hypertension. An average normal blood pressure may be assumed to be 120/80. Any rise above normal is likely to be gradual rather than sudden. At some point in this rise, treatment should be instituted. The longer treatment is delayed and the higher the pressure is allowed to rise before treatment is begun, the more likely are the arterioles to become sclerotic or calcified and the less satisfactory must be the results of treatment. If a pressure that tends to rise can be returned to normal in the early stages, there is a good possibility of preventing anatomico-pathologic changes; when such changes progress sufficiently far, they are irreversible.

In older persons, who have become accustomed to high pressure, especially if there be arteriolar sclerosis, caution must be observed in lowering pressures from any level.

In the beginning of studies to appraise hypertension, each patient should have a thorough study to discover and correct all possible factors that might influence the picture. Allergy, faulty digestion, hyperthyroidism and many other conditions may occasionally produce or intensify hypertension. Such conditions should be corrected and time allowed for improvement before any specific methods of treatment are instituted.

Bed rest may be necessary in the beginning of treatment because of vascular crises, threatened cardiac decompensation or other complications; otherwise, better results are obtained by avoiding too much bed rest: it has a bad psychologic effect on the patient. Early in the treatment, some rest may be indicated at various times during the day, but this is largely symptomatic treatment

and must be applied to the individual patient along with other general measures.

We use small doses of mild sedatives almost routinely in the treatment of hypertension. Our usual procedure is to give 0.5 gr. phenobarbital on rising and at noon daily. This takes the edge off the patient's nerves during the day and permits more satisfactory sleep during the night; by not giving sedatives at bedtime, there is less likelihood of a hangover the next morning. It is doubtful if worry and stress and strain are responsible for hypertension. However, patients with hypertension do worry excessively and are likely to live under high stress and strain. A small dose of sedative aids in the treatment. Frequently, especially in milder cases of hypertension, the sedative can be reduced or stopped after a few weeks as the pressure approaches normal.

Diet. A minimum of stress is placed on the kind of diet. The amount of food taken is of far greater importance than the selection of the diet. Overeating appears to play an important part in the maintence of pressure at a high level. We attempt to keep body weight as nearly normal as possible.

Almost all patients will show some drop in blood pressure on this regimen. After this has been followed until we are sure that no further improvement is to be expected, sulfocyanates may be given if the pressure is still too high. In this way, we have attempted to eliminate the danger of crediting psychic improvement to sulfocyanate therapy.

Sulfocyanate Therapy.—The potassium salt appears to be the form best suited for sulfocyanate therapy. It is not toxic in therapeutic doses, and it is given in larger doses than the sodium salt. As an initial dose we give 5 gr. daily, best given after breakfast. We do not give sulfocyanate to patients unless we are sure of securing a reasonable degree of coöperation.

This drug shows no tendency to the development of tolerance to its action. But there is a cumulative effect in many cases. For protection against this effect we make frequent determinations of the blood sulfocyanate concentration.[2,12] It is noteworthy that as the blood concentration of potassium sulfocyanate rises, blood pressure falls. At the beginning of its administration weekly blood tests appear to be adequate. Later, as the patient's response to the drug is better known, tests are made less frequently and still later at monthly intervals. We find that the lower the effective blood sulfocyanate concentration can be kept, the better the results. Many of our patients do best with a concentration of potassium sulfocyanate in the blood of 2.5 to 3 mg. per 100 cc. of blood which is within or near natural levels found without sulfocyanate therapy. Other patients require a concentration of 5 to 8 mg. or more per 100 cc. of blood. We use the lowest concentration that yields required results. No maximum concentration has been set, though

20 mg. per 100 cc. of blood is usually accepted as a high safe range. We have observed concentrations of 40 and 65 mg. per 100 cc. of blood with no serious ill effects. However, it appears that death may be produced at lower levels. To avoid untoward symptoms, pressures must be reduced slowly and gradually. The effects of sulfocyanates develop slowly and persist for a considerable time after therapy has been stopped. Frequently it is necessary to reduce the dose. Occasionally after several weeks it is necessary to increase the dose above 5 gr. daily. We have observed that with improvement in blood pressure and symptoms dosage may be reduced gradually after weeks or months of treatment.

The essential factor in treatment of hypertension is to furnish a sufficient amount of sulfocyanate to balance an unknown amount of pressor substance and maintain blood pressure at a satisfactory level. This level must depend on the degree of change in arterioles and capillaries, the cardiac reserve, and pressor substances.

Dangers. No contraindications to the use of sulfocyanates have been found. However, we always use it with care, especially in old arteriosclerotic patients. We do not expect to reduce extremely high pressures of long standing to normal levels. Such cases will require somewhat higher pressures than normal for at least several months. However, we find that almost every case will show a slow gradual fall over a period of several months. In angina pectoris, associated with hypertension, sulfocyanates can be used with care. A moderate and slow reduction of pressure tends to relieve angina. Sulfocyanates produce a prolonged effect instead of the fleeting effects of nitrites and demonstrate their superiority by reducing diastolic as well as systolic pressures.[2,5,12]

In cardiac decompensation we do not use sulfocyanates until compensation has been restored by rest in bed and such supportive measures as may be indicated. Then sulfocyanates are indicated. Cardiac decompensation is likely to appear in patients who have presented very high diastolic pressures.

In these cases, the heart has little opportunity to rest. The increased cardiac load results from increased peripheral resistance which in turn raises the diastolic pressure. Cardiac decompensation and failure are responsible for more than half the deaths of hypertensive patients. A lowered diastolic pressure makes recurrences of decompensation less likely. In apoplexy even slight lowering of the pressure tends to reduce the danger of recurrences.[2,3,5]

It has been noteworthy that in the sulfocyanate treatment of hypertension there is no tendency toward increased nitrogen retention in the blood. The assumption that sulfocyanates improve the circulation in the kidneys, especially in efferent vessels, has some justification.

Discussion. Sulfocyanate treatment is recognized as substitution therapy. It supplies sulfocyanate to a group of individuals who

suffer from high blood pressure and who also as a group have less sulfocyanate in the blood than other individuals.[4] The treatment apparently will be required for life.

Best results are obtained in less severe cases. Treatment should be started before there is too much sclerosis of the arterioles. Relief in hypertension by any method is possible only to the extent that spastic or sclerotic arterioles can be made to relax. After there is too much sclerosis there is grave doubt as to whether relaxation is possible.

Results. In our clinic in the past 4 years we have had a total of 136 hypertensives who have continued the treatment as long as 3 months. Shorter periods of treatment do not appear to be adequate for appraisal of the value of results. Symptomatic improvement seems to satisfy some patients and cause them to stop treatment. During the past 2 years, we have used smaller blood concentrations of sulfocyanates and have secured better results than formerly with higher concentrations.

We expect to get relief of symptoms in practically all cases. Functional results are good in two-thirds, while one-third show poor or fair results from treatment. Proper selection of cases for treatment would increase the percentage of good results almost to 100%. We feel that we are not justified in making such a selection because of the benefit from fair results and also from symptomatic improvement.

The underlying factor in failure is fibrosis of the arterioles and capillaries; this is seen in old arteriolar sclerosis itself as well as in syphilis, hemiplegia and cardiac decompensation. Fair results may be obtained in many of these cases by prolonged treatment. Difficulties have also been encountered in handling toxemias of pregnancy by this means.

Of our cases, 92 (67.7%) have been classed as showing good results, *i. e.*, showing a sustained reduction of at least 15% in both systolic and diastolic pressures (Table 1). Better results are obtained in private patients than in clinic and institutional cases (our private cases show 79% good results and 7% fair results) due to less syphilis, less vascular sclerosis, earlier diagnosis and treatment, and also to better coöperation. A large number of our cases show more than 15% reduction in pressures, many cases showing a normal pressure after some months. While 15% reduction is not dramatic, it is sufficient to relieve symptoms and decrease the danger of hemiplegia and angina.

There have been no deaths among our patients who were on treatment, or who had been on treatment. There has been 1 case of hemiplegia in a man who had secured symptomatic relief and stopped the treatment.

Our best results are obtained in those patients who show: 1, not too much change in arterioles and capillaries; 2, a low natural blood

sulfocyanate concentration; 3, satisfactory response to small doses of sulfocyanates; 4, a blood concentration of 2.5 to 5 mg. of sulfocyanate per 100 cc. of blood while on treatment; 5, full coöperation in the treatment.

TABLE 1.—RESULTS WITH POTASSIUM SULFOCYANATE

No. cases	Age group	Race		Sex		Results			Type of hypertension			Classification of patients*	
		W.	C.	M.	F.	Good	Fair	Poor	Essential	Luetic	Decompensation		
22	20–40	15	7	10	12	14	2	6	19	2	1	A—1 B—5	C—10 D—6
71	40–60	54	17	41	30	47	8	16	64	3	4	A—8 B—11	C—17 D—35
43	60–80	39	4	27	16	31	6	6	34	4	5	A—11 B—5	C—11 D—16
—		—	—	—	—	—	—	—	—	—	—		
136		108	28	78	58	92	16	28	117	9	10		
Per cent:						67.7	11.7	20.6					

Classification of results:
Good: Above 15% reduction in systolic and diastolic pressure.
Fair: Above 10% reduction in systolic and diastolic pressure.
Poor: Below 10% reduction in systolic and diastolic pressure.

* A—North Carolina State Hospital. B—North Carolina State Prison. C—Rex Hospital Clinic. D—Private patients.

Conclusions. 1. Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substance. The concentration is approximately 50,000 times that of nitrites.

2. Each individual has a fixed constant blood sulfocyanate level.

3. Blood sulfocyanate concentrations tend to vary inversely with the blood pressure level, whether naturally or under treatment.

4. There appears to be normally in the body a balance between pressor substances and sulfocyanates. There is a definite tendency for low blood sulfocyanate levels to be associated with hypertension. Higher concentrations of blood sulfocyanates are not associated with hypertension.

5. Potassium sulfocyanate is a safe depressor substance if used properly; it lowers the diastolic pressure as well as the systolic.

6. The earlier in the course of the disease that treatment is instituted, the better the results that can be anticipated.

7. The lower the effective blood sulfocyanate concentration can be kept during treatment, the better the results will be.

8. The results of this work show such a strong rationale for the use of sulfocyanates in hypertension that the use need no longer be regarded as empirical.

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THE EFFECT OF POTASSIUM THIOCYANATE ON THE OCCURRENCE OF MIGRAINE

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A study of the effect of thiocyanate on the occurrence of migraine headaches seemed of interest for two reasons: The first of these is the more recent understanding of the local mechanism responsible for the signs and symptoms of migraine, with emphasis on the supposition that all attacks of migraine begin with an excessive vasoconstriction of certain branches of the carotid artery. If this supposition be true, there would seem to be a possibility of preventing the attacks by the use of a long-acting vasodilator substance, such as potassium thiocyanate seems to be. The second reason for this study is the desirability of improving our present methods of treatment of migraine. There is no intention to review here such methods of treatment. The reader is referred to an excellent review of this subject by von Storch,[9] which is summarized in part as follows: "Therapeutic results are still far from satisfactory in migraine. Termination of individual attacks can be accomplished in most instances. The frequency and severity of attacks may be decreased in many cases. Complete relief is unusual." A more effective means of preventing migraine attacks would indeed be of considerable clinical value.

Although the apparent nature of the migraine mechanism has been long suspected on the basis of certain clinical observations, we are indebted to Wolff and his collaborators[5,8] for convincing experimental evidence on this subject. By means of special methods they were able to observe the caliber and pulsations of the temporal and middle meningeal arteries in relation to attacks of migraine. They found that the pain of migraine was associated with an increase in the amplitude of pulsations and the caliber of the

arteries. The relief from pain which followed the administration of ergotamine tartrate coincided with a diminution in the arterial pulsations and diameter; on the other hand, the increase in pain which followed injections of histamine was associated with an increase in the caliber and pulsations of the arteries. Thus, these and other observations by the same group of investigators constitute evidence that the pain of migraine is due to an excessive distention of extracranial and dural branches of the carotid artery.

These observations on the mechanism of pain in migraine may be less important clinically than a study of the vasomotor reactions associated with the pre-headache phenomena of this disorder. Of considerable significance may be the demonstration by Schumacher and Wolff[8] that under certain conditions the pre-headache scotomata of migraine could be abolished by the administration of the vasodilator substance amyl nitrite. From this observation one may infer that the initial vasomotor reaction, which occurs during the pre-headache phase of migraine, is one of excessive vasoconstriction of intracerebral vessels. In addition, it seems possible that initial vasoconstrictor reactions are not confined to intracerebral vessels, but involve the dural and extracranial vessels as well. It was on the basis of such a possibility that this study has been made—that is, to determine the effect of the vasodilator substance potassium thiocyanate on the frequency and severity of migraine.

Potassium thiocyanate was the chosen vasodilator drug for several reasons. It has been found to exert a prolonged depressor effect on the blood pressure of hypertensive patients in about half of the cases in which it has been employed.[1] This effect is seemingly due to peripheral vasodilatation because, first, the decrease in blood pressure occurs before any change in the composition of the blood,[7] and second, its effect on the blood pressure is enhanced following bilateral splanchnic and lumbar sympathectomy.[4] Furthermore, in our experience when potassium thiocyanate has been effective in reducing the blood pressure of a hypertensive individual, there has also been a definite decrease in the patient's response to the cold-pressor test. We regard this as evidence that potassium thiocyanate not only produces a mild peripheral vasodilatation in these cases, but in addition restrains the peripheral vasoconstrictor responses to stimuli of cold and pain. Since the advent of a method for the proper control of thiocyanate medication, as published by Barker in 1936,[2] it has been possible to give the drug intelligently with a minimum of risk. Recently Barker[1] and Kurtz[6] have separately reported their observations on the use of thiocyanate covering periods of 10 and 11 years, respectively. In their hands, serious reactions have been rare and fatalities charged to the drug have not occurred. However, other authors have attributed fatalities to the drug, even when given under controlled conditions. Attention

has been called to these reports by "Current Comment" in *The Journal of the American Medical Association*.[3] It is indisputable that the drug is potentially dangerous and should not be used without the necessary measures to control its blood concentration.

Material. The observations in this report were begun in November, 1940 (15 months ago) and are based on a study of 13 patients with migraine who have received potassium thiocyanate. The average period of observation for each patient has been 11 months. Patients who have been started on treatment less than 6 months ago have not been included in this report. Case histories have been kept as completely as possible, and, before compiling this report, answers to a detailed questionnaire were obtained from all patients included in this study.

The diagnosis of migraine was based on the following clinical considerations: All patients had been subject to attacks of severe headache with periods of complete freedom between attacks. In 11 of the 13 patients these attacks had been present since childhood or early adult life. A family history of "sick headache" was obtained in 11. In 10 patients the pain had been hemicranic. The pain, when severe, was of a throbbing character in 6. Nausea, with or without vomiting, was associated with the attacks of 10. In 2 patients manual compression of the carotid artery on the side corresponding to the pain brought temporary relief. In 10 women the attacks regularly occurred in close association with the menstrual flow.

Method. Two separate procedures were followed, depending upon the frequency of the migraine attacks experienced by the individual to be treated. First, patients who had been having migraine attacks as frequently as 3 times per month, or who had coëxisting hypertension, were instructed to take daily dosages of thiocyanate in the amounts of 6 gr. daily for 3 days, and then 3 gr. daily. After about 10 days the blood thiocyanate concentration was determined by the method of Barker.[2] No attempt was made to prescribe dosages of the drug that would produce optimum blood concentration of 8 to 12 mg. per 100 cc. as suggested by Barker for the treatment of hypertension. On the contrary, dosages were prescribed that would produce the lowest blood concentration effective against migraine.

Second, patients who had migraine attacks less frequently than 3 times per month and who could foretell the onset of an attack were advised to take 6 gr. of potassium thiocyanate when an attack seemed imminent. Because the drug was dispensed in enteric coated tablets,* patients were directed to crush the tablet in the mouth before swallowing. Four of the 13 patients were treated in this manner.

Patients whose attacks of migraine occurred less frequently than 3 times per month were not included in this study unless they could foretell the onset of attacks or had a coëxisting hypertensive disease.

Results. To facilitate description of results, we shall use the terms "mild headache" and "severe headache," with arbitrarily assigned definitions for each of these terms. "Mild headache" refers to a headache of mild discomfort and of less than 4 hours' duration. "Severe headache" designates a headache of greater severity and of longer duration. It will be appreciated that a "mild headache" is of minor consequence to the real migraine

* We are indebted to Eli Lilly Company for "Enseals" Potassium Thiocyanate used in this study.

sufferer. However, in the discussion that follows we shall include the mild headaches to describe the results more accurately.

Twelve of the 13 patients received substantial relief from migraine while taking thiocyanate. Of these 12, 4 patients obtained complete relief from headache of any description; 7 patients, who were relieved of severe attacks, experienced mild headaches with a frequency ranging individually from 1 to 8 times per month; 1 patient with an associated severe hypertension experienced an occasional severe migraine attack premenstrually. Only 1 of the 13 patients received no benefit from thiocyanate. In addition to migraine this patient suffered from severe allergic manifestations. She received daily dosages of potassium thiocyanate for 3 months with the blood thiocyanate concentration reaching 4.4 mg. per 100 cc.

TABLE 1.—EFFECT OF THIOCYANATE ON THE OCCURRENCE OF MIGRAINE

Case	Average frequency of migraine headaches per month: Before thiocyanate therapy "Mild"	Before thiocyanate therapy "Severe"	During thiocyanate therapy "Mild"	During thiocyanate therapy "Severe"	Daily dosage, gr.	Blood concentration, mg.	Period of observation, mos.
1*	0	2	0	0–1	4	7.5	15
2	0	12	0	0	3	2.3	15
3*	15	1–2	4	0	3	6.6	13
4*	8–12	0–1	0	0	6	6.2	12
5	0	6	1	0	3	...	2†
6	18	12	8	0	3	2.5	11
7	3–4	1–3	3–4	1–3	6	4.4	3†
8	22	8	4	0	6–9	4.5–8.3	8
9	0	10	0	0	3	3.4	7

* Migraine associated with hypertensive disease. See text.
† Discontinued thiocyanate therapy. See text.

In Table 1 is assembled data listing the approximate frequency and severity of headaches before and during thiocyanate treatment, the daily dosages employed, and the blood thiocyanate levels for individual patients who have taken daily dosages of the drug. It is noteworthy that 5 of 8 patients who were benefited required only 3 gr. of thiocyanate daily to obtain a satisfactory effect. The blood thiocyanate levels for these 5 patients ranged from 2.4 to 6.6 mg. per 100 cc. It is apparent that the blood levels of thiocyanate effective against migraine are substantially lower than those generally considered to be most effective in the treatment of hypertension. Three patients in the group had a coëxisting hypertension, which in no way seemed to alter the result of treatment.

An observation of considerable significance was afforded by the fact that 5 patients who had obtained relief from migraine while taking thiocyanate voluntarily discontinued the medication. In the case of 1 patient, severe headaches recurred only preceding the menstrual periods. The other 4 patients experienced a recurrence of headaches of approximately the same frequency and severity as obtained before treatment was begun. In each case the resump-

tion of thiocyanate medication again brought relief from the migraine attacks.

Case Report. The following case history is included because the extreme severity of the migraine experienced by this patient provided an excellent object for study.

A white male executive, age 45, had been subject to frequent "sick headaches" as long as he could remember. For several years he had had a mild attack daily, and severe attacks on the average of twice each week. During the latter he frequently had to be driven home from work and put to bed. In preceding years he had employed many forms of treatment, including large dosages of sedatives and vitamin B-complex, without relief. Sole relief was obtained from ergotamine tartrate taken at the onset of an attack. However, attacks thus aborted were prone to recur within a few hours, and at times he had taken 4 dosages of ergotamine tartrate daily. On the advice of his family physician this medication was discontinued.

When he presented himself for examination in June, 1941 (8 months ago) he was developing a right hemicranic headache. Pressure on the right carotid artery relieved pain. On the preceding day he had experienced a moderately severe left hemicranic headache, which possibly accounted for the well-developed periarteriolar sheathing observed in the fundus of the left eye. This finding was not present at a later examination. The right fundus appeared normal. The blood pressure was within normal limits, and the remainder of the physical examination revealed no important abnormality.

Thiocyanate medication was begun, and at the end of 2 weeks the blood thiocyanate level measured 6 mg. per 100 cc. The patient stated that contrary to instructions he had taken 6 gr. of thiocyanate daily. During this period he had had only 3 moderately severe headaches and on the remaining days had had no headaches at all so that he was much encouraged. During the next 6 weeks the patient took 9 gr. of thiocyanate daily, which resulted in an elevation of the blood thiocyanate concentration to 8.3 mg. per 100 cc. During this period he experienced an average of 1 to 2 mild headaches weekly. There had been 1 severe headache. He estimated the degree of relief as about 90%.

After continuing this program for about 2 months, the patient voluntarily discontinued the medication for 2 weeks, during which there was a recurrence of frequent violent headaches. During the next 2 weeks he endeavored without success to obtain relief by taking 6 gr. of thiocyanate at the very onset of the headaches. Whereupon, a daily dosage of 6 gr. of thiocyanate was resumed. Two months later the blood thiocyanate measured 4 mg. per 100 cc., and the patient reported that he had been having an average of 1 mild headache weekly. Violent headaches had not occurred.

The results obtained by the second group of patients—those who have taken thiocyanate only when a migraine attack seemed imminent—can be described briefly. One patient, who had been subject to a severe attack of migraine preceding each menstrual period for years, has over a period of 10 months been able to prevent the occurrence of headaches by taking 6 gr. of thiocyanate daily for 2 or 3 days preceding the menses. There were 2 women who had each been subject to an average of 2 severe attacks of migraine monthly. One of these has been able over a period of 6 months to prevent the headaches by taking 6 gr. of thiocyanate at the

onset of pre-headache symptoms consisting of "extreme tension." The other patient was able to prevent the headaches from becoming severe by taking 6 gr. of thiocyanate at the very onset of the attack. However, this patient discontinued this procedure after 2 months because of untoward symptoms consisting of "uneasiness around the heart" and "pain in my hemorrhoids and varicose veins." The fourth patient in this group, a salesman, age 35, had experienced severe headaches on an average of 2 a month and milder headaches about 3 times monthly for several years. Over a period of 11 months he has been able to prevent the occurrence of headaches by taking 6 gr. of thiocyanate at the onset of prodromal symptoms, which, he declared, are too vague to be described.

Several patients have experimented with taking thiocyanate after the onset of headache. In all instances thiocyanate taken in this way has failed to bring relief. It must, therefore, be emphasized that for thiocyanate to be effective in preventing attacks of migraine it must be taken in daily dosages or taken during the pre-headache phase of the attack.

Comment. The observations herein reported indicate that potassium thiocyanate, properly administered, is effective in reducing the frequency and severity of migraine headaches.

The success of thiocyanate in reducing the frequency and severity of attacks of migraine is, in the light of present knowledge of the drug, probably due to its prolonged vasodilator action. Should this supposition be true, it would constitute additional evidence that the initial vasomotor reaction in migraine is one of excessive vasoconstriction of the involved branches of the carotid artery, and it would establish the logic of employing long-acting vasodilator drugs in the treatment of migraine. However, it is possible that the effectiveness of thiocyanate in the treatment of migraine depends upon some unknown action of the drug—a consideration which emphasizes the speculative nature of the above reasoning.

The clinical value of potassium thiocyanate in the treatment of migraine cannot at present be fully determined. The excellent results observed in this study would seem to justify its trial in the following groups of patients; first, those patients who by their ability to foretell the onset of attacks can obtain a satisfactory result with the use of small quantities of the drug; second, those who suffer a degree of morbidity from migraine sufficient to justify the daily administration of the drug; and lastly, those migraine sufferers who have an associated hypertensive disease.

However, a decision to employ thiocyanate in the treatment of migraine must take into consideration the potential toxic properties of the drug. The effects of overdosage with thiocyanate have been clearly described[1,7] and can be prevented by the use of certain safeguards in the administration of the drug. But even so, there is still the question of possible harmful effects from the prolonged

administration of the drug. It is encouraging that the experiences of others,[2,4] who have employed the drug in the treatment of hypertension for more than a decade, have not furnished evidence of ultimate deleterious effects from the prolonged intelligent administration of the drug. However, it is recognized that a longer period of observation will be necessary before reaching a final conclusion on this very important question.

Summary. Potassium thiocyanate in daily dosages sufficient to produce a blood concentration of the drug of 2.5 to 8 mg. per 100 cc. is effective in reducing the frequency and severity of migraine headaches. Potassium thiocyanate in 6 gr. dosages taken during the pre-headache phase of a migraine attack is useful in aborting the headache. On the other hand, potassium thiocyanate taken after the onset of actual headache is of no value.

The rationale of treating migraine with the use of long-acting vasodilator drugs is discussed. The possibility of harm resulting from overdosage or long-continued administration of a potentially dangerous drug, such as potassium thiocyanate, in the treatment of migraine, has not been entirely eliminated, though positive evidence is still lacking.

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THE LOCALIZING VALUE OF THE CLINICAL, ELECTROENCEPHALOGRAPHIC, AND PNEUMOENCEPHALOGRAPHIC FINDINGS IN EPILEPSY

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It is the purpose of this paper to compare the relative values of the clinical study, the electroencephalogram (E.E.G.), and the pneumoencephalogram (P.E.G.) for the localization of focal cerebral lesions in convulsive disorders. The electrical seizure patterns in cases of symptomatic epilepsy will be compared with those in patients with idiopathic epilepsy, and the effects of hyperventilation upon

the inducement of these waves noted. The variations in the alpha, beta, and delta waves, also the pneumoencephalographic abnormalities present will be described; also our findings as to the correlation of these abnormalities with any significant changes in the E.E.G.

Studies upon the comparison of the clinical signs, E.E.G. and P.E.G. observations have been made by Yeager *et al.*,[45] Davidoff,[8] Rheinberger and Siris,[36] Goldensohn, Marmor and Meyer.[22]

In this series of 52 cases, 24 (46.2%) were classified as idiopathic epilepsy. Of these 24, there were 18 (75%) with seizure patterns. These 18 cases consisted of 6 instances of grand mal, 6 petit mal, and 11 of psychomotor epilepsy. Four patients had a combination of 2 or more seizure patterns, hence are listed twice in the preceding classification.

Twenty-eight patients (53.8%) of the entire series had symptomatic epilepsy. The symptomatic group was classified as follows: traumatic in 8 (15.2%); brain tumor in 5 (9.6%); mental deficiency, dating from birth and of undetermined origin in 6 (11.5%); vascular lesions in 4 (7.7%); congenital communicating hydrocephalus in 3 (5.8%); encephalitis in 1 (1.9%); and porencephalus in 1 (1.9%).

In this symptomatic group there were 14 (50%), who had seizure patterns. These seizure patterns consisted of 7 grand mal, 2 petit mal, and 8 psychomotor. In 2 patients there were 2 or more of these seizure patterns present. It thus may be noted that the occurrence of seizure patterns in the symptomatic epilepsy group was 21.2% less than in the idiopathic group.

In the entire group of 52 patients there were 32 patients (61.5%) in whom E.E.G. seizure patterns were present; whereas in 20 (38.5%) they were absent. In 6 cases, 2 or more types of seizure patterns existed. Grand mal patterns were found in 13 instances (23.4%); psychomotor waves in 19 patients (36.5%); petit mal in 7 (13.4%); and 6-cycle waves in 4 cases (7.7%).

In order to verify the existence of epilepsy during the latent period, artificial means of precipitating these convulsive patterns, or even of bringing on the convulsions, should be utilized. Hyperventilation is the most simple of these methods. In this series 16 were hyperventilated, and in 12 (75%) specific seizure patterns were so induced. These seizure patterns were: grand mal 3, petit mal 3, psychomotor 5, and combinations of these in 1.

In addition to the specific epileptic patterns present in the E.E.G., there were certain other abnormalities. Increased beta voltage was present in 13 cases (25%), 16 cases (30.8%) showed unequal alpha, 31 patients (59.6%) had delta patterns, and 12 cases disclosed increased beta voltage combined with delta pattern. In only 2 instances was the E.E.G. entirely normal; both cases were traumatic.[15,16,17,29]

When unilateral lesions did not involve the occipital lobe, it has been reported that the affected side showed a much stronger alpha rhythm (Lemere).[28] In our series, 16 patients showed differences in the alpha between the two occipital areas. In 8 of them the strongest alpha was on the side of the lesion, and in an equal number it was on the other side. In none of these cases was a lesion of the occipital lobe indicated.

In 33 patients delta and seizure waves originated in a circumscribed area of the brain. Such an E.E.G. is defined as a focal E.E.G. In 6 cases there were 2 or more foci in widely separated regions of the brain that gave rise to delta and seizure pattern, and these were termed cases of multiple foci. There were 11 patients in which the delta and seizure waves alternated with normal wave patterns in all areas in the brain. This type was called "diffuse foci."

In 8 instances, 15.4%, a normal P.E.G. was found, while in 44 (84.6%) some abnormality was noted. These abnormalities was noted. These abnormalities consisted of unequal ventricles in 35 patients (67.3%), decreased cortical air in 18 patients (34.6%), hydrocephalus in 11 (20.4%), increased cortical air in 11 (20.4%), ventricular shift in 9 (17.3%), subdural air in 2 (3.8%), dilated third ventricle in 2 (3.8%), and a very small ventricle in 1 patient (1.9%).

In those patients with unequal ventricles the E.E.G. did not demonstrate any consistent pattern. In those cases in which there was decreased cortical air, there was no pattern diagnostic of such a change upon E.E.G. examination.

Increased cortical air markings interpreted as atrophy occurred in 11 instances (20.4%). Rubin[38] found it was possible to localize atrophy of the cerebral cortex in schizophrenic patients by comparing the alpha rhythms of the various regions of the two hemispheres with each other. His findings were confirmed by P.E.G. in 8 out of 9 patients. Our study did not verify Rubin's observations.

Ventricular shift was present in each of 9 patients (17.3%). Ventricular shift is caused by mass-displacing lesions, such as tumor, abscess or hemorrhage; by cerebral atrophy or cerebral cicatrix. In the mass-displacing lesions the shift is to the opposite side of the lesion, whereas in atrophy or adhesions there is a shift to the side of the lesion.[4,5,14,37] In 5 of these cases there was a mass-displacing lesion, and in 4 of them atrophy and cerebral cicatrix was present. In all 9 the E.E.G. accurately localized the side of the lesion.

Hydrocephalus may be of a communicative or obstructive type. Obstructions may exist in the third ventricle, aqueduct, or subarachnoid channels. In this group there were 11 cases with hydrocephalus, 3 being of the congenital communicating type. In only

1 case was a focal lesion demonstrated both by clinical and E.E.G. observation. In none of these was a focal lesion demonstrated by the air studies. Two of this group showed unequal ventricles. The E.E.G. demonstrated grand mal attacks in 2 instances, psycho-

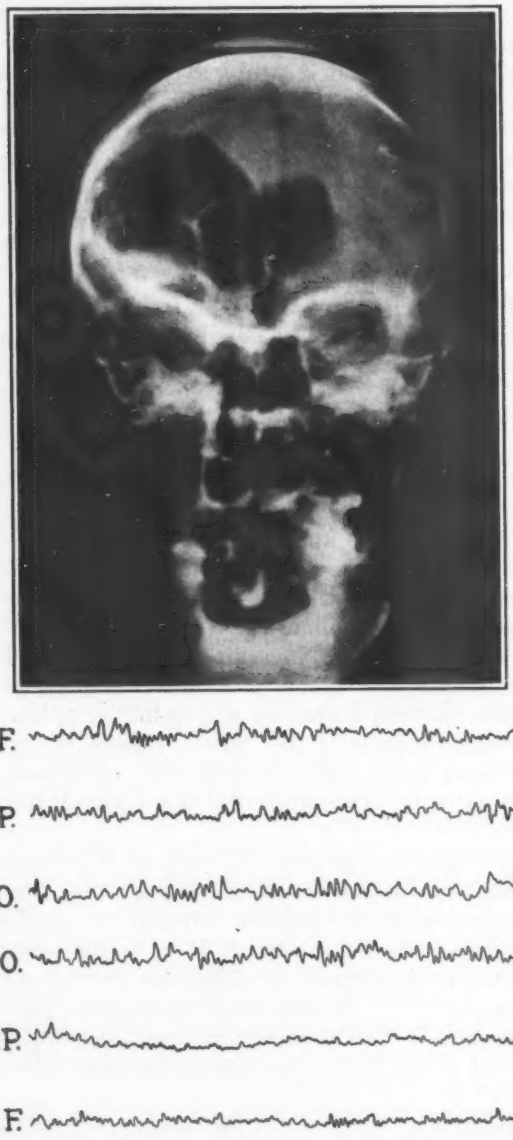


FIG. 1.—Case A. S. Porencephalic cyst with generalized epilepsy. The E.E.G. (electroencephalogram) shows grand mal waves in the left occipital and parietal region with irregular alpha on the right side. The P.E.G. (pneumoencephalogram) shows a porencephalic cyst in the right frontal region.

motor in 1, irregular alpha in 1, increased beta in 1, and diffuse abnormalities in 2. In the entire group of 11 cases, 4 demonstrated a superimposed beta on the delta with an increased beta voltage. This was also present in the 1 case of porencephalus (Fig. 1).

In the series, the E.E.G. localized lesions in 33 cases (63.3%), the clinical findings in 31 (59.3%), and the air studies in 9 cases (17.2%).

Localized abnormalities of the E.E.G. occurred in the prefrontal and premotor areas in 10 patients; motor area, 5; parietal-temporal, 5; occipital, 5; suprasellar, 3. Clinical signs localized lesions in the prefrontal and premotor areas in 2 cases, motor area in 26, suprasellar in 3. The P.E.G. localized lesions in the prefrontal and premotor areas in 2 instances; motor area, 3; suprasellar, 3; occipital, 1. It is quite apparent that in cases of convulsive disorders lesions are not found as frequently in the parietal-temporal and occipital areas as they are in the frontal lobe.

In this entire series of cases there were 31 patients (59.6%) who had clinical focal epilepsy, and 21 patients (40.4%) who had clinical non-focal epilepsy.[12]

In 10 of the 31 cases of clinical focal epilepsy, the E.E.G. and the clinical signs localized the lesion in the same lobe. In 7 of the 10 cases the P.E.G. also localized the lesions in the same lobe. In 9 patients the clinical findings and the E.E.G. localized the lesion on the same side, but the E.E.G. did not coincide with the clinical signs as to lobe involvement. In 2 of these 9 cases the P.E.G. and the clinical signs accurately localized the lesion, but the E.E.G. failed to do so. In 3 patients the clinical findings and the E.E.G. findings localized the lesions in entirely different places. In 7 instances in which the clinical signs definitely localized a single lesion, the E.E.G. showed abnormal electrical activity throughout the brain. In 1 case wherein the clinical signs definitely localized the lesion, the E.E.G. showed 2 separate areas of abnormal electrical activity, and in 1 case the clinical signs localized a lesion while the E.E.G. was normal.

In the 21 cases in which the clinical signs showed no evidence of focal epilepsy, the P.E.G. also failed to demonstrate a focal lesion. The E.E.G., however, showed 13 cases in which the area of abnormal electrical activity was confined to one lobe; 3 instances of multiple foci, and 4 instances of the diffuse type. There was only 1 patient who had an entirely normal E.E.G.

The E.E.G. was a definite aid in the localization of cerebral dysfunction. When the clinical findings and the air studies failed to demonstrate the area of abnormality within the brain substance, the E.E.G. frequently gave us evidence as to the location of the affected area.

Without the use of the P.E.G. many cases of convulsive seizures would be classified as idiopathic epilepsy because the exact intra-

cranial pathology is not apparent upon clinical study. The P.E.G. aids in segregating such cases as tumors, traumatic or porencephalic cysts, cerebral atrophies and cicatrix, and obstructive and communicating hydrocephalus of varying grades.[20,21,42]

In 24 patients of idiopathic epilepsy, the P.E.G. revealed 16 with unequal ventricles, 4 slight hydrocephalus, 5 decreased cortical air, 5 increased cortical air, 1 case of subdural air, and 4 normals. The abnormalities found in idiopathic epilepsy have been reported by others.[2,7,10,13,23,25,26,30,31,43]

The E.E.G. showed 6 patients with grand mal, 5 petit mal, 11 psychomotor, 8 unequal alpha, 3 increased beta, and 3 diffuse delta. None of these patients had normal E.E.G. Thirteen patients (42%) demonstrated focal abnormalities by clinical signs, while the P.E.G. failed to localize any specific lesion.

Traumatic epilepsy may be focal or generalized. In cases of depressed fracture or gunshot wounds a local area of the brain is destroyed and there is a tendency toward focal convulsions (Glaser and Shafer).[18] The percentage of patients with generalized convulsions associated with cerebral concussion and trauma is low (1.8%) (Glaser and Shafer).[19] Trauma may produce generalized hydrocephalus, localized areas of cortical atrophy, or meningocerebral cicatrix (Foerster and Penfield),[14] with migration of the ventricles toward the lesion and traumatic cysts.

There were 8 cases of traumatic epilepsy in this series (Fig. 2). In 6 cases (88%) both the E.E.G. and the clinical findings accurately localized the lesions. In 3 of these the P.E.G. confirmed the diagnosis. The P.E.G. abnormalities consisted of 7 instances of unequal ventricles, with 3 of these 7 having a shift to the side of the lesion, 3 air, 1 subdural air and 1 traumatic cyst.[34] The P.E.G. was abnormal in all 3 patients, with traumatic epilepsy. The E.E.G. examination indicated 2 cases of grand mal, 1 psychomotor, 5 unequal alpha, 2 increased beta, and 2 normal. These 2 patients were the only ones with normal E.E.G. in the entire series.

Convulsive seizures are frequently associated with brain tumor. Sargent,[40] in 240 cases, reported 30% of the patients with brain tumors developed epilepsy, while Parker[32] in 313 cases reported 21.6% developed epilepsy. Penfield, Erickson and Tarlov,[33] in 703 cases of brain tumor, reported that the occurrence of convulsive seizures depended upon the location of the tumor as well as the pathology. Convulsive seizures were found in 37% of all intracranial tumors and 45% of all supratentorial tumors. Dowman and Smith[9] reported 39% had convulsions, of which 21% were focal in character. Sachs and Furlow[39] found 34% of the patients with tumors developed convulsions, while Peterman[35] reported 29% developed convulsions.

The accuracy of the E.E.G. in localization of brain tumors has been reported by Jasper[24] to be in the neighborhood of 90% to 95%;

Baldes *et al.*[1] reported 86% accuracy. The localization of cerebellar, suprasellar and other subcortical lesions by the E.E.G. is still in the experimental stage.[41,44]

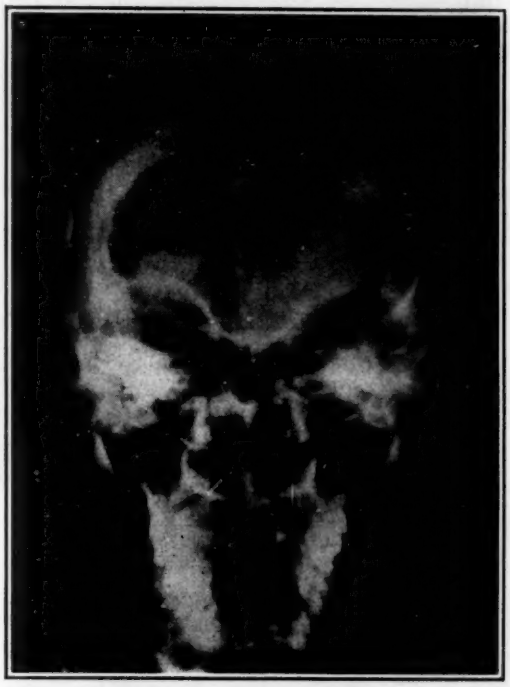
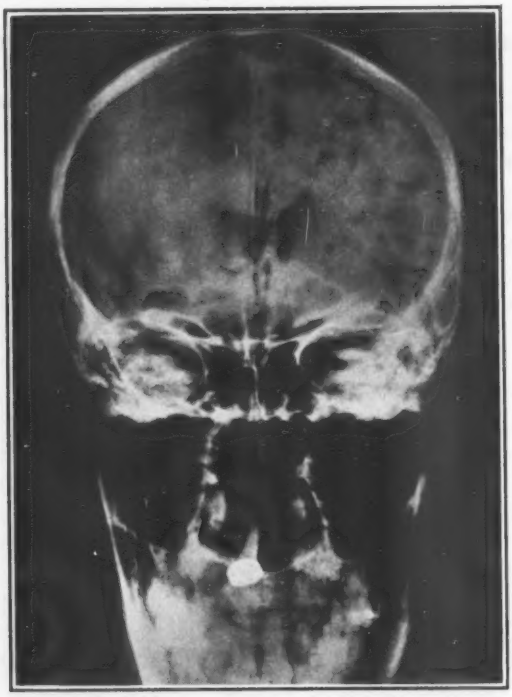


FIG. 2.—Case E. R. Depressed skull fracture over the right motor area with right hemiparesis. The epileptic seizures were generalized, but the E.E.G. demonstrated grand mal waves originating from the left motor area, thus coinciding with the clinical localization. The P.E.G. demonstrated a dilated left lateral ventricle with a shift to the left.

The E.E.G. in this series of 5 cases of brain tumor showed psychomotor waves in 1 case, irregular alpha in 1, increased beta in 2, diffuse abnormalities in 2 (Figs. 3 and 4). The air studies indicated



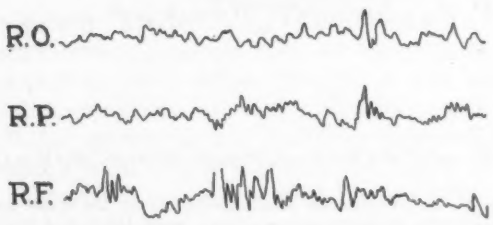
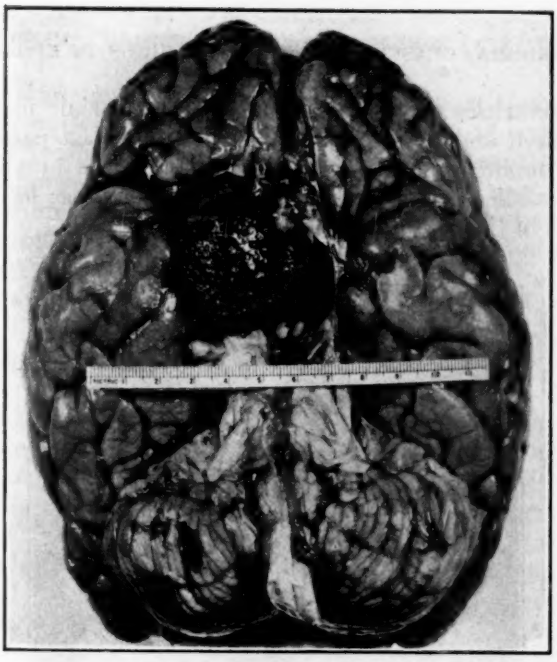
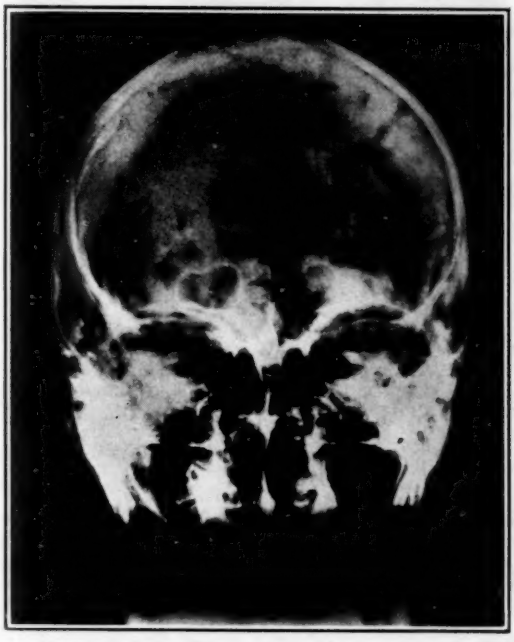


FIG. 3.—Case M. B. Meningioma situated in the right motor area directly in midline with focal epileptic seizures. The E.E.G. and the P.E.G. all localized the lesion accurately.

LEGEND FOR FIG. 4.

FIG. 4.—Case I. R. The patient had a large sphenoidal ridge meningioma situated on the right side, the epileptic seizures were focal in character. The E.E.G. localized a deep-seated lesion in the right frontal area. The P.E.G. also indicated a deep-seated lesion situated over the right base.





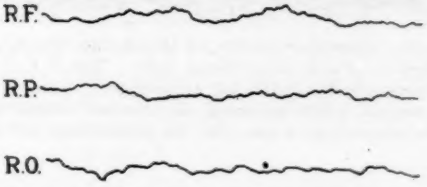


FIG. 4.—(For legend see opposite page.)

unequal ventricles in 3 cases, decreased cortical air in 3, hydrocephalus in 1, and a normal P.E.G. in 1. This last patient had a pituitary tumor. Focal lesions were demonstrated by clinical and electrical studies in 5 patients, while the air studies localized the lesions in 4 of them.

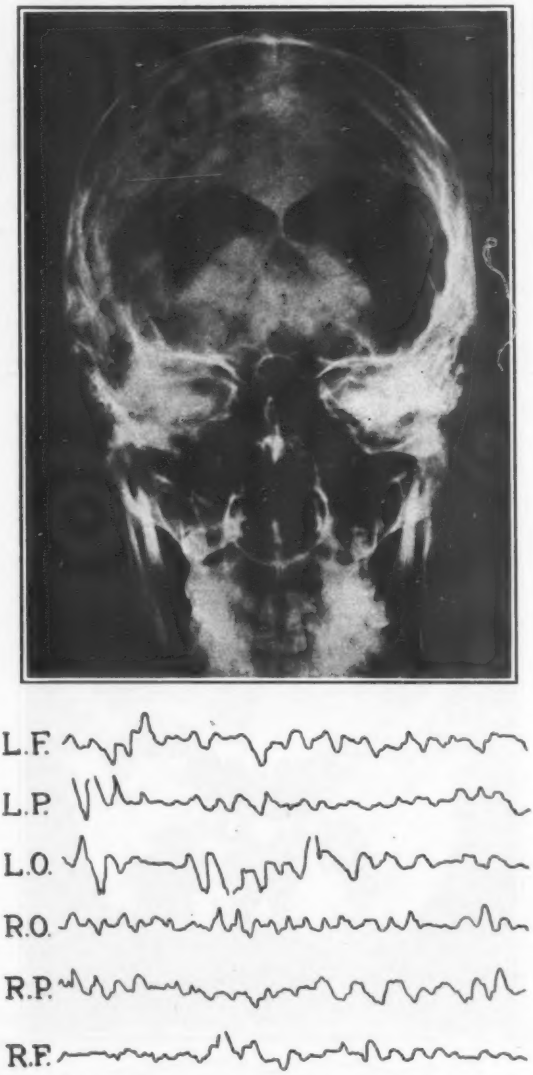


FIG. 5.—Case H. G. Dilatation of the ventricles (left side larger), with atrophy due to a vascular lesion. Focal convulsions (left). The E.E.G. shows grand mal and psychomotor waves over the entire left hemisphere. This coincided to a certain degree with the air studies, which indicated that the left lateral ventricle was larger than the right. It is interesting to note that the patient had left-sided focal attacks.

There is a group of children and infants with mental and physical retardation whose nervous system shows evidence of cerebral damage, which presumably dates from birth. The exact etiology of such conditions is difficult to ascertain, but they may be due to some vague intra-uterine condition, to degenerative diseases, developmental defects, anoxemia, or other causes of uncertain origin.

The conventional diagnosis of feeble-mindedness, or cerebral palsy, does not define the anatomical defect, or the physiologic residue. The P.E.G. may be entirely normal, or demonstrate certain anatomic changes within the brain. These abnormalities consist of variations in the size and shape of the ventricles, and the subarachnoid space. The dilatation of the ventricles in these cases is rarely due to obstruction, but is usually caused by atrophy with a compensatory enlargement.[3,6,11,27]

Six mentally defective children had focal lesions demonstrable by the E.E.G. in 5, by clinical signs in 4, and in none of them by the air studies. The P.E.G. findings consisted of 4 cases of unequal ventricles, 1 with slightly dilated ventricles, 2 with decreased cortical air, 1 with increased cortical air and 1 normal. E.E.G. findings were abnormal in all 6 cases. The abnormalities were petit mal 1, psychomotor 3, unequal alpha 1, and diffuse delta in 1.

Cerebralvascular lesions consisting of thrombosis or embolus may cause a local atrophy with the resulting dilatation and migration of the ventricles, cysts, dilatation of both ventricles and cortical atrophy. In some instances the ventricular system may be entirely normal. In the 4 cases of this series, 2 patients had unequal ventricles, as well as increased cortical air. The other 2 patients had entirely normal P.E.G. The E.E.G. revealed 1 case of grand mal, 2 cases of psychomotor patterns, and 3 instances of diffuse delta activity. In 3 instances the clinical signs demonstrated focal lesions, while the E.E.G. and the P.E.G. only demonstrated a focal lesion in 1 case (Fig. 5).

Summary. 1. The electroencephalogram (E.E.G.) pointed to focal epilepsy in 33 of our 52 cases (63.3%); the clinical findings in 31 (59.6%); and the air studies in 9 (17.2%).

2. The pneumoencephalogram (P.E.G.) was normal in 8 cases (15.4%) and the E.E.G. was normal in 2 cases (3.8%).

3. Of 32 patients, 61.5% had seizure patterns upon electroencephalographic examination. We would expect a greater number of seizure patterns if it had been possible to hyperventilate each case.

4. Of the 52 cases, 24 (46.2%) were classified as idiopathic epilepsy, of which 18 (75%) had seizure patterns; 28 (53.8%) had symptomatic epilepsy of which 14 (50%) had seizure patterns.

5. Delta patterns were present in 31 (59.8%); unequal alpha in 16 (30.8%); increased beta voltage in 12 (23.5%).

6. From a clinical standpoint, 31 patients (59.6%) had focal epilepsy, and 21 patients (40.4%) had generalized epilepsy.

7. The E.E.G. demonstrated areas of abnormal activity in 30 of the 31 cases of focal epilepsy, and 20 of the 21 cases of non-focal epilepsy. In those with non-focal epilepsy, the E.E.G. was the only evidence that areas of abnormal activity existed in the brain.

8. In the cases of this series the abnormalities, as indicated by the three tests, were more frequently located in the frontal lobes.

9. Patients with either idiopathic or symptomatic epilepsy presented the same types of clinical convulsions and the same types of electrical seizure patterns; and hyperventilation induced all types of seizure patterns.

10. The P.E.G. demonstrated ventricular shifts in 9 cases. The E.E.G. localized the side of the lesion in each instance. Specific electroencephalographic abnormalities were not found in patients with increased or decreased cortical air or unequal ventricles. Severe hydrocephalus showed increased beta voltage combined with delta.

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THE EFFECT OF SULFONAMIDES UPON ARTIFICIAL FEVER PRODUCED BY PEPTONE IN ANIMALS*

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The investigation reported here represents a delayed study of a clinical antipyretic action noted in the late spring of 1936 with two sulfonamides, "P.T. 353," and "P.S. 364" later called Prontosil and Prontosil-Soluble, provided through the courtesy of Professor H. Hörlein in May, 1936. The fall in febrile body temperatures seen in those early days suggested that these drugs might be acting upon the hypothalamic temperature centers. Substantiating this suggestion were the early toxicologic studies of Halpern and Mayer,[1] which indicated that large doses of sulfonamides (sulfanilamide) had a subcortical site of action in the central nervous system. A marked fall in the normal body temperature of mice, rats, guinea pigs, rabbits and cats has been reported with large, lethal or sublethal doses of sulfonamides by several authors.[2] In all of these animal experiments, the dose of sulfonamides employed was a very large one, being many times the maximal therapeutic dose per unit body weight as used in human therapeutics, and it is quite possible that the lowering of body temperature was part of a shock syndrome which may accompany the administration of excessive amounts of many drugs.

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There is abundant evidence that sulfonamides reduce febrile temperatures in animals or patients host to those infections toward which the sulfonamides are specific chemotherapeutic agents. There is little experimental evidence to indicate whether these drugs in therapeutic doses act upon the temperature-controlling mechanism of the body *per se* or upon the pathogen producing the fever. Beeson and Janeway[3] gave various sulfonamides to rabbits in doses which were not stated in relation to body weight but which would probably correspond to about 0.5 gm. per kilogram by mouth and they got little effect upon normal body temperature or upon artificial fever produced by typhoid vaccine. The drugs were also injected intravenously and then it was found that sulfapyridine had an antipyretic action in rabbits. The number of animals used was not stated.

Method. Experiments will be described in which various sulfonamides were given by mouth (stomach tube) at a dose of 0.1 gm. per kilo body weight of albino rats, rabbits and cats. Each experiment consisted of a group of 4 animals whose rectal temperatures were recorded at intervals of ½ hour throughout the day. The first animal was given an intramuscular injection of 1 gm. of peptone per kilo body weight and 2 hours later, when body temperature was rising rapidly to febrile levels, a sulfonamide was given by stomach tube. The second animal was given peptone only. The third animal received no peptone but was given the same sulfonamide and at the same time as animal number one. The fourth animal received neither peptone nor sulfonamides. This experiment was repeated to a total of at least 10 times with each sulfonamide and the mean changes in rectal temperature were then plotted against time.

Results. *Sulfanilamide.* Sulfanilamide had no outstanding effect either upon normal body temperature or upon the febrile temperature of peptone fever in rabbits. A number of normal rabbits showed a slight febrile reaction to sulfanilamide 4 or 5 hours after giving the drug. Sulfanilamide also had no antipyretic action toward peptone fever in albino rats. The rectal temperature of the albino rat was found to decline irregularly during the morning hours and the resulting curves were not as steady as for rabbits. Peptone produced a good artificial fever in cats and sulfanilamide had no antipyretic effect toward this fever. In normal cats, sulfanilamide produced quite a pronounced febrile reaction. These results demonstrate that sulfanilamide in a dose of 0.1 gm. per kilo by mouth, usually the maximal human therapeutic dose, has no antipyretic effect toward peptone fever in albino rats, rabbits and cats but that it may have a febrile effect upon normal body temperature.

Sulfapyridine. The results with sulfapyridine were somewhat variable. In rabbits sulfapyridine sometimes had an antipyretic effect toward peptone fever and at other times no effect. On the average, there was a slight decline in the peptone febrile temperature

after giving this drug. The differences between rabbits may have been due to differences in the rate of gastro-intestinal absorption of the drug since sulfapyridine is well known to be erratically absorbed from the intestinal tract. Sulfapyridine had no effect upon the normal body temperature of rabbits. In the albino rat sulfapyridine had no effect upon normal body temperature nor upon artificial fever induced by peptone. The different responses of rabbits on the one hand and albino rats on the other may be related to the greater susceptibility of rabbits than albino rats to sulfonamides.[2]

Sulfathiazole. Sulfathiazole in doses of 0.1 gm. per kilo had no effect upon the normal body temperature of rabbits nor upon the febrile temperature of peptone fever. A similar result was obtained in the albino rat.

Sulfadiazine. Sulfadiazine, provided through the courtesy of the American Cyanamid Company, had no antipyretic effect toward peptone fever in rabbits and no effect upon normal rectal temperature in the dose employed.

Sulfaguanidine. Sulfaguanidine was provided through the courtesy of E. R. Squibb and Sons of Canada, Limited, and it was found to have no effect toward peptone fever in rabbits and no effect upon normal body temperature.

Parabenzylsulfanilamide. Parabenzylsulfanilamide was provided by Poulenc Frêres of Canada, Limited. It is variously known as Proseptazine, Septazine, M and B 125 and 46 R.P.[4] In rabbits it had no antipyretic action toward peptone fever and no effect upon normal body temperature.

Parasuccinylsulfanilamide. Parasuccinylsulfanilamide was provided some years ago through the courtesy of Gedeon Richter, Limited, of Budapest, under the name of Ambesid. It had no antipyretic action toward peptone fever in rabbits but produced a definite and marked rise in normal body temperature.

Promin. Promin, the sodium salt of p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate, was provided through the courtesy of Parke, Davis & Company. It had a slight pyretic effect in normal rabbits but no effect upon peptone febrile temperature.

Sulfacetamide. Sulfacetamide is sulfanilamide with the amide nitrogen acetylated and should not be confused with the acetylated sulfanilamide of blood and urine during sulfanilamide therapy. The latter substance has the acetyl group attached to the para-amino nitrogen. Sulfacetamide was used in Europe in 1938 under the name Albucid and has recently been introduced into Canada under the name Sulamyd; it was provided through the courtesy of Schering (Canada), Limited. It had no antipyretic action toward peptone fever but had a mild febrile effect upon normal rabbits.

Sulfanilyl-dimethylsulfanilamide. Sulfanilyl-dimethylsulfanilamide is one of the disulfanilamides also known as Diseptal C, Disulon and more commonly in Europe as Uleron or Uliron[4] where it has had extensive trial in the therapy of gonorrhea. It was provided through the courtesy of the Winthrop Chemical Company. It was found to have no effect upon the body temperature of normal rabbits nor upon the febrile temperature of rabbits given peptone.

Azosulfamide. Azosulfamide is the second sulfonamide described by Domagk and is known under various synonyms[4] such as Prontosil Soluble, Neoprontosil and Streptozon-S. It is a red, water-soluble azo compound provided through the courtesy of the Winthrop Chemical Company. It was found to have no effect upon peptone febrile temperature in rabbits but had a pronounced febrile reaction in normal rabbits given by mouth and, as with the other sulfonamides, at a dose of 0.1 gm. per kilo body weight.

Sulfonamide EOS. Sulfonamide EOS is the paramino sodium ethyl sulfonate of sulfanilamide. It is a palatable, water-soluble sulfonamide, especially useful in treating infants. It was provided through the courtesy of Imperial Chemical Industries, Limited, of Manchester, England. This sulfonamide also had no effect upon peptone fever nor upon normal body temperature of rabbits given in doses of 0.1 gm. per kilo by stomach tube.

Summary. Sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfaguanidine, parabenzylsulfanilamide, parasuccinylsulfanilamide, promin, sulfacetamide, sulfanilyl-dimethylsulfanilamide, azosulfamide and sulfonamide EOS were given by mouth in doses of 0.1 gm. per kilo body weight to rabbits and, in some instances, albino rats and cats, with an artificial fever induced by the intramuscular injection of peptone and with suitable controls. Body temperature was recorded rectally at intervals of 0.5 hours.

The only sulfonamide which, at this dose, had any antipyretic effect toward peptone fever was sulfapyridine, and it exhibited this effect only upon some rabbits and not at all in albino rats.

Sulfanilamide, parasuccinylsulfanilamide, promin, sulfacetamide and azosulfamide were found to exhibit varying degrees of pyrexia in normal animals.

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ALCALIGENES FÆCALIS BACTEREMIA

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The *Alcaligenes fæcalis* group of organisms is generally classified as being intermediate in their morphologic and cultural characteristics between the colon and the Brucella groups. They are generally considered to be saprophytes and non-pathogens.

Petruschky (1896) first isolated the organism from human feces and stale beer. Standard textbooks of bacteriology[18] describe the *Alcaligenes fæcalis* organisms as Gram-negative rods, variable in size and usually larger and thinner than *B. coli* and the ends are less rounded. The organisms are motile and may show peritrichate flagella. Colonies grow well on agar slants and show a raised central portion and a spreading undulate edge. Neither gas nor acid is produced in any of the usual carbohydrate fermentation tests or substrates. Litmus milk is rendered alkaline and a brown pigment is produced on potato media which is characteristic. However, it is generally conceded that these organisms are not a sharply defined group.[12]

Pathogenicity. It seems to be well established that *Alcaligenes fæcalis* on occasion can be definitely pathogenetic. It may give rise to a variety of disease conditions. For example, meningitis has been reported by Spray and Hawk,[16] also by Gatewood,[3] and Mason.[9] Anderson[1] cultured the organism from the blood of 2 patients who exhibited a syndrome simulating rheumatic polyarthritis. The organism was found in the blood of a patient with acute hepatitis and jaundice by McIntyre.[10] An Alcaligenes type bacillus was cultured from the blood of a patient with a typhoid-like state by Hazen and Mortillaro,[5] and others,[14] and also from cases of acute gangrenous appendicitis by Emil Weiss.[20] It was considered the cause of death in a case of protracted sepsis reported by Goldberg.[4] Gall stones[2] and a renal calculus[17] were found to harbor the organism. The bacillus has been considered the pathogenic agent in certain types of infant summer diarrheas[19] as well as the cause of a few cases of adult enterocolitis.[15] Positive stool cultures have been reported in a few cases of convalescing typhoid fever and bacillary dysentery.[6] The close morphologic and cultural relationship between certain strains of the *Bacillus alcaligenes* group and the bacillary organisms associated with dog distemper has been pointed out.[13]

Case Report. The patient, a white male, aged 36, was admitted to the hospital on June 15, 1941, complaining of diffuse epigastric pain and fever

of 3 days' duration. His wife and 5 children were in good health. He had worked as a baker during his entire adult life in a small town north of New Orleans.

On physical examination his temperature was 101.6°, pulse 110, B.P. 125/80, and respiration 20. He was well developed and well nourished. There was no lymphadenopathy. The heart and lungs were negative. No abdominal tenderness could be elicited and the spleen could not be palpated. The genitalia and the extremities were likewise negative.

During his first hospital stay which lasted about 8 weeks the patient had a remitting type of fever which ranged from 99° in the morning to 101° to 103° in the evening. Several times a week the patient experienced shaking chills. The epigastric pain lasted 3 days and was followed by a dragging sensation in the left hypochondrium which persisted in a varying degree for 18 days. The spleen was palpable for a short time during this period.

Agglutinations for typhoid, paratyphoid, undulant fever, tularemia and bacillary dysentery were negative. The skin test for undulant fever was negative; the urine and stool were negative, on culture as well as microscopic examination.

The red blood cell count was 3,660,000 and the hemoglobin 12 gm. The white blood cells numbered 5400 (60% neutrophils with a moderate shift to the left). Multiple smears of the blood were negative for malaria. The chest Roentgen ray film was negative. Of 6 blood cultures, 4 yielded no growth, but 2, collected on July 16 and 17, were positive for an organism which grew well on brain broth, 5% dextrose agar, lactose agar, and beef infusion agar. The organisms were slightly motile Gram-negative rods which showed moderate variation in size. No fermentation occurred in dextrose, lactose, sucrose, maltose, mannite, rhamnose, xylose or dulcital. Litmus milk was alkalinized in 4 days, and gelatin was slightly liquefied in 24 hours. The colonies on agar were discrete and grayish and 1 to 2 mm. in diameter in 24 hours. On the basis of these findings the organisms were tentatively classified as belonging to the *Alcaligenes fæcalis* group. An agglutination test using the patient's serum and the culture organisms was found to be negative. As the attending staff felt that these organisms were probably contaminants, and the clinical picture closely resembled malaria, it was decided to try a course of quinine. Quinine sulphate was given in therapeutic doses. There was a sudden drop in the patient's temperature to normal which lasted until the time of discharge on August 15. He was instructed to continue quinine medication at home.

The patient was readmitted to the hospital on August 21, 1941. He stated that while at home he was without fever for 2 days, then the fever (102°) returned each afternoon, preceded by a chill. After 3 days of chills and fever, he decided to return to the hospital. During this second admission which lasted 39 days, the patient's condition grew progressively worse. Anemia, toxemia and anorexia were now present and there occurred a 30 pound loss in weight.

The red blood cell count was 3,300,000; hemoglobin 9 gm. The white blood cell count was 8000 (82% neutrophils). The urine showed occasional granular casts and a few white blood cells and red blood cells. Cystoscopy was performed on September 4, because the patient had complained of tenderness in his right flank. Urine cultures from each kidney and retrograde pyelograms proved negative. Proctoscopy revealed a normal bowel. The tuberculin test 1 to 1000 O.T. was also negative. The agglutinations were repeated and again found negative. The skin test and the opsonocytophagic index for undulant fever were again reported negative. Six blood cultures failed to show a growth but 2 were positive for an organism having the characteristics of *Bacillus alcaligenes fæcalis*.

The patient was given sulfanilamide 60 gr. for 3 days then 30 gr. daily thereafter. There was a drop in temperature to normal for 3 days with a subsequent evening elevation of about 100°. The patient was discharged on September 29 with a low-grade fever. Sulfanilamide was discontinued on the day of discharge.

The patient remained at home for 20 days and the fever continued with a small afternoon rise to 100°. Eight days before the third admission the fever reached 105° and was associated with chills and sweats. On October 20 he again sought admission. At varying times while at home he experienced severe aching pain of the left chest with the ascent of fever. Later there was aching of the left fourth toe and small toe but no swelling of the joints. The ball of the left foot was swollen and tender for 2 days.

On admission the spleen could be palpated and a soft systolic murmur could be heard at the apex. Sulfanilamide was started the day after admission but was discontinued 13 days later as it seemed ineffective. For 10 days he received no medication and then sulfadiazine 15 gr. q.i.d. was begun and continued until time of discharge on December 19. There was a drop in the temperature to normal 8 hours after the initial dose, and except for slight elevations to 100° on 3 occasions, it remained normal. During the time that the patient was receiving sulfanilamide medication he had pain and swelling of the right ankle joint which lasted 2 days. Five days later there was tenderness and pain of the left knee and hip joint but no swelling. This subsided in 3 days. Swelling and pain of the first and second right metacarpophalangeal joints were present on November 15 and 16, during sulfadiazine therapy.

On November 29 the patient complained of headache and on the following day the headache was more severe with definite stiffness of the neck and suggestive Kernig's and Brudzinski's signs were present. Spinal puncture revealed a pressure of 250 mm. of water with normal mechanics. The fluid was hazy and contained 1000 cells per c.mm. with 65% polymorphonuclears and 25% lymphocytes and 10% unidentified cells. No organisms were present on smear or culture. Fever of 100° to 101° was present, but 2 days later the temperature was normal, and 4 days later all suggestive meningitic symptoms had disappeared.

During the third and last admission all of the usual laboratory procedures were repeated. This included agglutinations, urine and blood counts. All were reported normal. Six blood cultures were done and all were negative except one obtained on October 20. This culture was positive for *B. alcaligenes fæcalis* which made a total of 5 positive blood cultures for this organism. Gastro-intestinal Roentgen rays were normal and roentgenograms of the joints and large bones were negative.

The patient was discharged on December 19 as afebrile and with no complaints. During the 2 weeks prior to discharge he had gained 15 pounds in weight. He was readmitted on January 31, 1942, for a checkup. The patient was afebrile. The blood counts were normal. There had been a progressive gain in weight and the patient felt well.

Comment. This case is of interest because of the long duration (4 months) of the febrile course and the multiplicity of the symptoms. In the majority of the other cases reported in the literature which we were able to study, the duration of the septicemia ranged from 2 weeks to 2 months. The striking symptoms in our case were the shifting polyarthritis which developed during October and involved successively the toes of the left foot, right ankle joint, left knee and hip joints and the right metacarpophalangeal joints. These symptoms closely resembled those reported as occurring in

Anderson's cases.[1] The joints showed local redness, heat, pain, and slight swelling but there was no evidence of joint damage. Of interest also were the development of signs and symptoms as well as laboratory evidence of meningitis which occurred during the second week of sulfadiazine therapy. In the 3 reported cases of *Alcaligenes fæcalis* meningitis, 1 occurred following an otitis media,[16] another complicated a meningocele,[9] and the third followed a craniotomy.[3] These cases suggest the possibility that trauma to the central nervous system paved the way for invasion by the mildly pathogenic *Alcaligenes fæcalis* although this was not true in our case.

Many reports have pointed out the similarity between *B. alcaligenes fæcalis* septicemia and mild typhoid and paratyphoid fever. In our case, the persistent fever, slowly progressive toxemia, low white count, mild anemia, splenomegaly, and increased erythrocyte sedimentation rate were all suggestive. Marshall[8] has stated that many cases of clinically mild typhoid or paratyphoid fever which the laboratory fails to confirm, if studied carefully, will prove to be *Alcaligenes fæcalis* infections. We are inclined to agree with this statement. It is of interest to note that Ravenel[14] reported finding lesions typical of early typhoid fever in an autopsy of a patient dying of *Alcaligenes fæcalis* bacteremia.

At various times during his illness the patient had pain in the right flank, and on November 13 the urine was reported positive for white and red blood cells. The same findings were noted on several subsequent examinations and although repeated urine cultures were negative, we felt we were justified in assuming that a low-grade urinary infection was present, which was probably due to the same organism isolated from the blood stream. Stuart, Thompson and Krikorian[17] reported a case of urinary tract infection in which the organism was cultured from the urine; they were also successful in isolating the *B. alcaligenes fæcalis* from a stone removed at operation from the left kidney.

Many bacteriologic texts express doubts that specific agglutinins develop in patients with *B. alcaligenes fæcalis* infections; however, Wyatt and Stuart,[21] also Thompson and Krikorian[17] and others have found agglutinins present in low titer. Our case did not show agglutinins.

We are at a loss to explain the varied responses to the therapeutic agents used. Quinine was used empirically with what was thought at first to be a good result; however, the subsequent course of the illness proved rather definitely that this drug was of no value, and that the drop in temperature was not due to the specific effect of the quinine. Sulfanilamide was without any prolonged effect since fever as well as other symptoms of the illness persisted in spite of the presumably adequate dosage.

All symptoms of the illness promptly disappeared after the administration of sulfadiazine. This of course excepts the episode

of meningitis which occurred after 18 days of sulfadiazine therapy. Five blood cultures have been reported negative since the use of the drug, and on follow-up examinations during a 3-month period, the patient has been found to be asymptomatic. However, it is a question in our minds whether sulfadiazine had anything specific to do with the ultimate recovery of the patient.

Summary and Conclusions. A case of bacteremia due to a *Bacillus alcaligenes fæcalis* type organism has been presented. The bacteremia and fever lasted for 4 months; the interesting manifestations were a polyarthritis and meningitis. Following the use of sulfadiazine the symptoms disappeared and the blood cultures became sterile.

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THE EFFECT OF THE HYDROGEN-ION AND STARCH CONCENTRATION OF THE SUBSTRATE ON SERUM AMYLASE AND AMYLASE-ACCELERATOR OF SERUM

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A starch-splitting ferment, diastase, or more accurately, amylase, was first found in the blood by Magendie in 1846.[7] It apparently is partly or wholly of pancreatic origin, and its amount is increased by ligation of the pancreatic ducts,[6] and is increased or decreased by pancreatic disease, cysts and tumors.[3,4,5,13,14]

The great variability in the observations on the amylase content of the blood serum may be ascribed, in part at least, to the various methods used,[4] and especially by the reaction and the concentration of the substrate. As may be seen in Table 1, in which are

TABLE 1.—EFFECT OF THE HYDROGEN-ION CONCENTRATION ON THE STARCH-LIQUEFYING AND AMYLASE-ACCELERATING ACTIVITY OF NORMAL HUMAN SERUM.

pH of starch substrate	Percentage concentration of starch substrate (and date of titration)	Amylase units*a* in normal human serum (per cc.)	Amylase units per cc. of duodenal contents *b*	Amylase units in same duodenal contents + 0.3 cc. normal human serum *e*	Amylase-accelerating units per cc. of normal human serum	Percentage increase in amylase units produced by 0.3 cc. normal human serum
3.0	6 (1/9)	+*h*	+*h*			
4.0	6 (1/9)	+				
4.8	6 (2/13)	0	30.8	204.0*f*	571.6	562
5.0	6 (1/16)	0	27.0	102.4*g*	248.8	280
5.6	2 (12/1)	11.3				
5.7	4 (2/4)	+	141.2	296.4	512.2	110
5.7	6 (1/7)	+	75.0*c*	80.0*c*	16.5	7
6.0	6 (1/9)	1.5				
6.2	6 (1/13)	+	141.2	200.0*f*	194.0	41
6.2	6 (1/16)	..	160.0	184.4*g*	80.5	15
6.3	4 (2/4)	..	204.2	235.2	102.3	15
6.4	6 (1/9)	0				
6.8	4 (2/4)	..	214.4	300.0	282.5	40
7.0	6 (1/9)	+				
7.0	4 (2/9)	+	220.8	371.2	496.3	68
7.0	4 (2/16)	+	31.1*d*	79.4	159.4	155
7.2	6 (1/13)	+	220.0	120.0*f*	−330.0	−45
7.2	6 (1/16)	+	150.0	252.8*g*	339.2	69
7.3	4 (2/4)	..	207.2	287.2	266.6	39
7.8	6 (1/13)	..	120.0	80.0*f*	−132.0	−33
7.9	6 (1/16)	+	75.0	141.2*g*	218.5	88
8.0	6 (1/9)	14.2				
8.0	4 (2/4)	..	77.6	196.8	393.4	154
8.6	6 (1/13)	+	47.2	80.0*f*	108.2	69
8.6	6 (1/16)	..	45.0	84.0*g*	128.7	87

a A unit of amylase is the amount which requires 60 minutes to produce a 20% reduction in the viscosity of a starch substrate.[5,8,12]

b 0.1 cc. of duodenal contents (except 2 titrations *c*, *d*) and 0.3 cc. water were added to 10 cc. of 2% to 6% starch suspensions and the amylase activity determined viscometrically at 34° C.[5,8,12] The duodenal contents were collected 12/3 from an infant, kept in a refrigerator, and diluted 1 to 4 with saline before being titrated (H. L. H. No. 40773, 18 months of age, normal digestion, diarrhea during the previous summer).

c Amylase units per cc. of 1% taka-diastase (diluted with saline). In the serum amylase-accelerating titration, the enzyme and serum were mixed 15 minutes before being added to the starch suspension.

d Amylase units per cc. of 0.2% holadin (diluted with saline).

e 0.1 cc. of the same duodenal contents *b* and 0.3 cc. pooled normal human serum were mixed and (except in 11 titrations *c*, *f*, *g*) immediately added to 10 cc. of 2% to 6% starch suspensions, and the amylase-accelerating activity determined viscometrically at 34° C.[9]

f The amylase activity of 0.3 cc. serum was titrated for 90 to 120 minutes at 34° C., and then 0.1 cc. duodenal contents was added to the mixture, and its amylase activity retitrated at 34° C. The final reaction of the pH 4.8 mixture was pH 5.6, and that of the pH 8.6 mixture was pH 8.2.

g 0.1 cc. of the duodenal contents was mixed with 0.3 cc. pooled normal human serum 30 minutes before being added to the starch suspensions.

h + indicates that amylase was present, but that it was less than 1 unit per cc.

tabulated the results of 25 viscometric titrations[2,8,12] of the amylase in pooled normal human serum at hydrogen-ion concentrations from 3.0 to 8.6, the amount of serum amylase is irregularly affected by the reaction of the substrate. At pH 4.8, 5.0, and at 6.4, no serum amylase could be demonstrated, and only at pH 5.6, 6.0 and 8.0 were the amounts sufficient to record in units.[2,8,12] The variation in these results also was increased by differences in the concentration of the substrate (2% to 6% starch).

In addition to amylase, human serum contains an amylase-accelerator,[1,9,10,15] *i. e.*, the addition of serum to duodenal contents increases their starch-liquefying activity to a greater degree than can be explained by the amylase content of the added serum (Table 1). This amylase-accelerating strength of normal human serum is greatest at pH 4.8. Large amounts also are present at pH 5.0, 5.7, 7.0 and 8.0; it is apparently absent at pH 7.2 and 7.8. The optimal reaction of human duodenal contents is pH 7.0.[11]

Conclusion. Serum amylase and amylase-accelerator results in order to be comparable should be obtained by titrations made at the same reaction, and with the same preparation and concentration of starch.

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THE SIGNIFICANCE OF THE SO-CALLED P–PULMONALE PATTERN IN THE ELECTROCARDIOGRAM*

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The clinical recognition of cardiac involvement due to chronic lung disease has recently been aided by radiologic studies,[27] includ-

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ing direct visualization[28,36] of the chambers of the heart, and by the use of ether for determination of the pulmonary circulation time.[25] However, little attention has been paid to the electrocardiogram in this condition. The majority of authors[2,4–9,11,21,30,35,37,39] reporting on the electrocardiogram have discussed the presence or absence of changes in the ventricular complex indicative of strain on the right ventricle. The first to draw attention to the occurrence of typical changes in the P waves in bronchial asthma was Kahn.[16] M. Winternitz[40] described a characteristic pattern of the P wave in the limb leads, consisting of a small upright P in Lead I and tall upright peaked P waves in Leads II and III, all of normal duration; this combination was designated as P-pulmonale and the changes were attributed to strain on the right auricle. This contour contrasts with the broad notched upright P_1 and P_2 characteristic of left auricular strain seen particularly in cases of rheumatic mitral stenosis.

This P-pulmonale pattern has in recent years been noted by various authors,[10,12–14,17,18,20,23,24,26,27,29,31,33] but there has been no unanimity as to its frequency or diagnostic significance. Parkinson and Hoyle[27] found this pattern in only 4 of the 60 cases of emphysema. Harkavy and Romanoff[14] described 15 such cases in their series of 50 patients with bronchial asthma and drew attention to the transitory nature of this contour which occurred only during the asthmatic attack in the majority of cases. Nordenfelt[23,24] denied the specific significance of this P pattern and claimed that such P waves occurred frequently in the absence of pulmonary disease in individuals having a labile sympathetic nervous tone.

This discrepancy in the literature suggested the present study in which the incidence, constancy and diagnostic value of this P-wave pattern was analyzed by selecting 50 consecutive cases with this contour and determining the clinical and, where available, the autopsy findings.

Criteria Employed. The 50 consecutive records were obtained from the routine tracings taken in the Heart Station during the past 2 years which fulfilled the following criteria:

1. P waves of normal duration (less than 0.12 second) and without notching.
2. P_3 taller than P_1.
3. P_1 small and upright (less than 1.5 mm.).
4. P_2 and P_3 tall and peaked (greater than 2 mm.).
5. P in CF_2 inverted and greater than 1.5 mm.
6. P in CF_4 inverted.

TABLE 1.—CLINICAL AND ROENTGEN RAY CORRELATION IN 50 CASES SHOWING THE P–PULMONALE PATTERN

Clinical evidence of pulmonary disease		Roentgen ray evidence of pulmonary disease			Clinical and/or Roentgen ray evidence of pulmonary disease	
Yes	No	Yes	No	No films taken	Yes	No
35	15	32	10	8	40	10*

* No films taken in 3 cases.

TABLE 2.—POSTMORTEM CORRELATION OF CHRONIC PULMONARY DISEASE IN 8 AUTOPSIED CASES OF P-PULMONALE

Case	QRS in limb leads	Deviations of S-T segment	Pathologic findings in heart: Wall, left vent., cm.	Wall, right vent., cm.	Wt., heart, gm.	Other findings	Pulmonary pathologic findings
1	Left ventricular preponderance	...	1.0	0.1	340	Moderate coronary sclerosis. Fatty infiltration of myocardium of right ventricle	Pulmonary emphysema. Healed apical tuberculosis.
2	Small QRS_1; diphasic QRS_2 and QRS_3 and deep S_2 and S_3	...	1.0	0.2–0.3	400	Hypertrophy and dilatation of right auricle and ventricle	Pulmonary emphysema. Moderate pulmonary arteriosclerosis.
3	No axis deviation	$S-T_2$ and $S-T_3$ depressed	1.2	0.1	175	Brown atrophy	Pulmonary emphysema.
4	Right axis deviation	$S-T_2$ and $S-T_3$ depressed	1.2	...	200	Hypertrophy of right ventricle. Brown atrophy of left ventricle	Bronchiectasis. Pulmonary emphysema.
5	Small QRS_1; diphasic QRS_2 and QRS_3 and deep S_2 and S_3	...	1.0	0.3–0.8	300	Marked hypertrophy and dilatation of right ventricle. Dilated left auricle. Enlarged pulmonary conus	Pulmonary emphysema.
6	Small QRS_1; diphasic QRS_2 and QRS_3 and deep S_2 and S_3	...	...	...	500	Hypertrophy and dilatation of right ventricle. Obliteration of pericardial sac. Myocardial fibrosis	Pulmonary emphysema. Pulmonary arteriolosclerosis.
7	Small QRS_1; diphasic QRS_2 and QRS_3 and deep S_2 and S_3	...	1.4	0.2–0.4	360	Moderate hypertrophy of right and left ventricle. Fatty infiltration of right ventricle	Pulmonary emphysema.
8	No axis deviation	$S-T_2$ and $S-T_3$ depressed	1.4	0.2	350	Moderate coronary sclerosis. Myocardial fibrosis	Pulmonary emphysema.

Results. The results are summarized in Tables 1, 2 and 3. In Table 1 is shown the frequency of clinical and Roentgen ray evidence of pulmonary disease. In Table 2, the necropsy findings in 8 cases are presented.

TABLE 3.—ANALYSIS OF THE VENTRICULAR COMPLEX IN 50 TRACINGS SHOWING P–PULMONALE PATTERN*

Right ventricular preponderance		11
Right axis shift		13
With depressed S–T in Leads II and III	7	
Without depressed S–T in Leads II and III	6	
Left axis shift		3
Left ventricular preponderance		5
No axis shift		10
With depressed S–T in Leads II and III	7	
Without depressed S–T in Leads II and III	3	
Small QRS_1 with diphasic QRS_2 and QRS_3 and deep S_2 and S_3		5
Intraventricular block		3
S type	2	
Common type	1	
Total		50

* Patterns are described in Katz.[17]

The pattern of the ventricular complexes in the 50 cases of P-pulmonale are listed in Table 3. Right ventricular preponderance, characterized by a mainly inverted QRS in Lead I with a prominent S wave, was present in only 11 cases (Fig. 1 *A* and *B*, Fig. 3 *A*). However, depression of the S–T segment in Leads II and III, which may be an indication of right ventricular strain, occurred in 7 of 13 cases of right axis shift (Fig. 1 *C*) and in 6 of the 10 cases without axis deviation (Fig. 3 *B*). The evaluation of such S–T depressions is, however, difficult since the tall P_2 and P_3 tends to be followed by a prominent auricular T wave causing a depression of the P–Q segment which extends into and depresses the S–T segment. Furthermore, in some cases, digitalis and/or coronary insufficiency had to be considered as a possible cause of the S–T depressions. Low "voltage" in the limb leads was present in 1 case, and a tendency to low "voltage" in 5 additional cases (Fig. 1 *C*).

Leads CF_2 and CF_4 were available in all cases. P was inverted in both leads, more deeply in position C_2 than in C_4 (Fig. 1 *A*, *C*, *D* and *E*, Fig. 2 *A* and *B*, Fig. 3 *A* and *B*). In contradistinction to the prolonged diphasic, and unusually large P in mitral stenosis, in P-pulmonale the auricular wave in CF_2 consists of a single inverted phase of normal duration.

Analysis of the 50 cases showing the P-pulmonale pattern in the electrocardiogram revealed evidence of chronic pulmonary disease on clinical and/or roentgenologic examination in 40 instances (Table 1). Right ventricular preponderance was present in only 9 instances. Chronic cor pulmonale is often associated with hypertension or coronary disease which in itself leads to left ventricular hypertrophy, and in such cases there is a combination of right and

left ventricular strain. Furthermore, Scott and Garvin[34] have shown in a series of 50 autopsied cases of cor pulmonale that even in the absence of an associated hypertension, coronary sclerosis, or valvular lesion, hypertrophy of the muscle was not limited to the right ventricle alone, but occurred simultaneously in both. This may explain the low percentage of right ventricular preponderance found

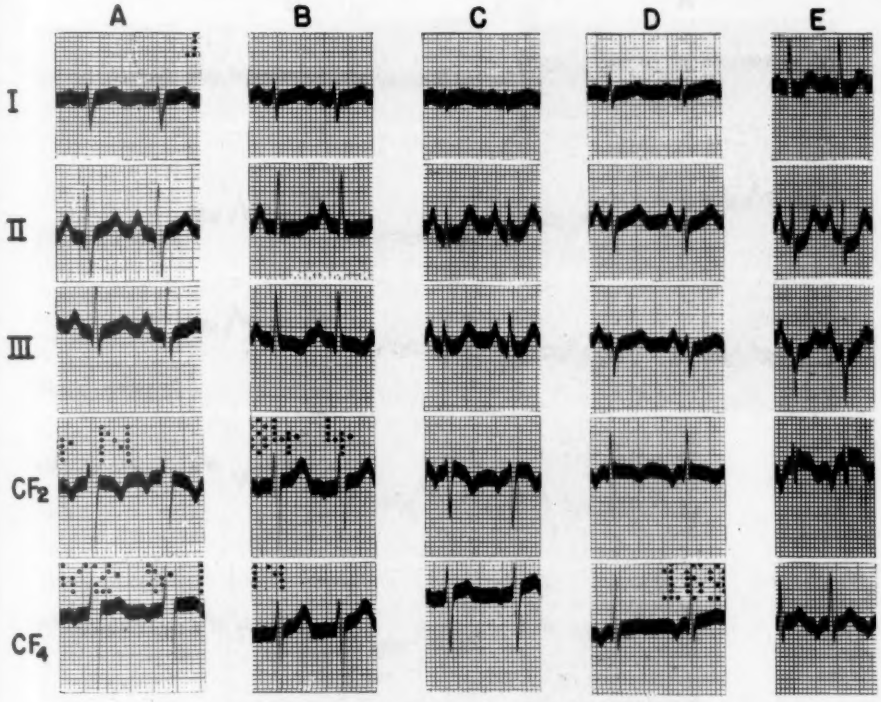

FIG. 1.—Five examples of P-pulmonale and the chest lead equivalent associated with P-pulmonale. Discussed in text. *A*, A case of pulmonary emphysema shows right ventricular preponderance and T inversion in CF_2. *B*, A case of bronchial asthma also shows right ventricular preponderance. *C*, A case of pulmonary emphysema shows right axis shift with marked S–T depression in leads II and III as well as T inversion in CF_2. *D*, A case of bronchiectasis and arteriosclerotic heart disease shows small QRS_1 and diphasic QRS_2 and QRS_3 with deep S_2 and S_3 as well as QRS upright and T inverted in CF_2. *E*, A case of pulmonary emphysema shows left ventricular preponderance of the mixed type with marked S–T depression in Leads II and III as well as small QRS and inverted T in CF_2.

in our series. The combination of right and left heart strain may give rise to the peculiar pattern observed in 5 cases, characterized by a small diphasic QRS in Lead I, and a mainly inverted diphasic QRS in Leads II and III with deep S_2 and S_3 (Fig. 1 *D*). This configuration resembles the QRS limb lead pattern produced by anterior wall infarction but can be differentiated from it.[15]

In the 10 cases of P-pulmonale without clinical or Roentgen ray

evidence of pulmonary disease the QRS duration and "voltage" were normal. The ventricular complex was normal in 5 cases. One case showed the pattern of anterior wall infarction, 1 showed changes suggestive of acute cor pulmonale (middle tracing of Fig. 2 *B*), 1 had S–T depressions in Leads II and III (Fig. 3 *B*) and 2 showed right ventricular preponderance.

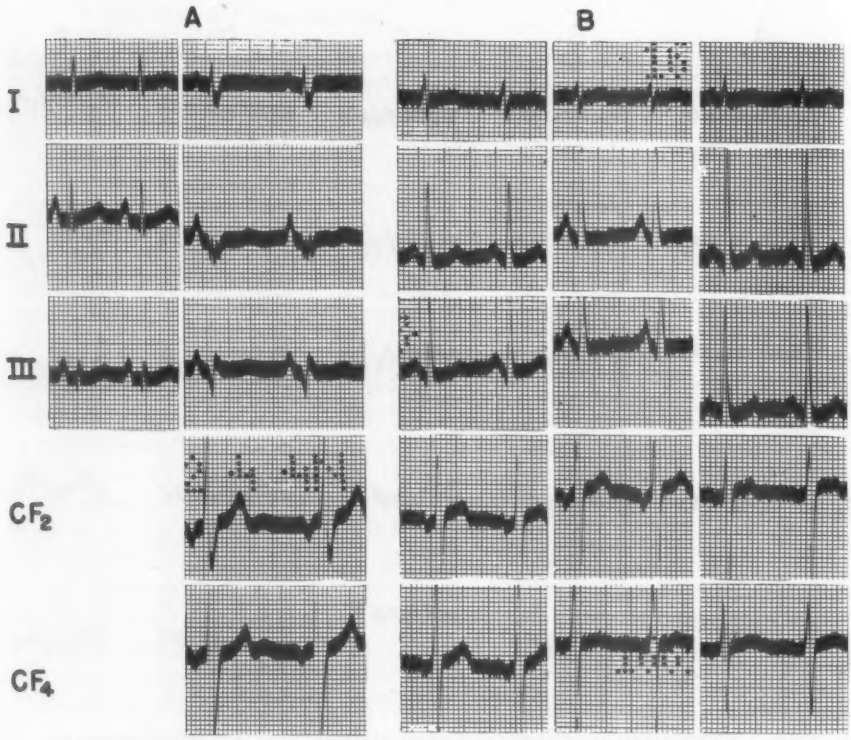

FIG. 2.—*A*, The 2 records of P-pulmonale were taken in a case of bronchial asthma and pulmonary emphysema, 9 years apart. The first record shows P-pulmonale with left axis shift. The second record shows the persistence of the P-pulmonale with its chest lead equivalent and the development of intraventricular block of the S-type. Discussed in text. *B*, The 3 records are from a case of postoperative pulmonary embolism. In the first record, taken within a few hours of the clinical episode there is a right axis deviation. This persists in the second record taken 6 days later, and is associated with T-wave changes and the development of P-pulmonale and its equivalent in CF_2. Practically all these deviations have disappeared in the third record taken 2 weeks after the second, confirming the view that all the changes including those of the P wave were due to an acute cor pulmonale. Discussed in text.

The 10 cases with P-pulmonale but without evidence of chronic pulmonary disease included a case of congenital heart disease with pulmonic stenosis (Fig. 3 *A*), 1 of carcinoma of the rectum with a clinical episode diagnosed as pulmonary embolism (Fig. 2 *B*), 1 of recent myocardial infarction of the anterior wall pattern, 1 of hyper-

thyroidism, and 6 cases diagnosed as psychoneurosis or psychosis (Fig. 3 *B*). In the first 3 of the 10 cases, it is possible to explain P-pulmonale on the basis of permanent pulmonary hypertension (pulmonic stenosis) or transient pulmonary hypertension (acute cor pulmonale, recent myocardial infarction) leading to right auricular strain.* In the remaining 7 cases, however, the change in the

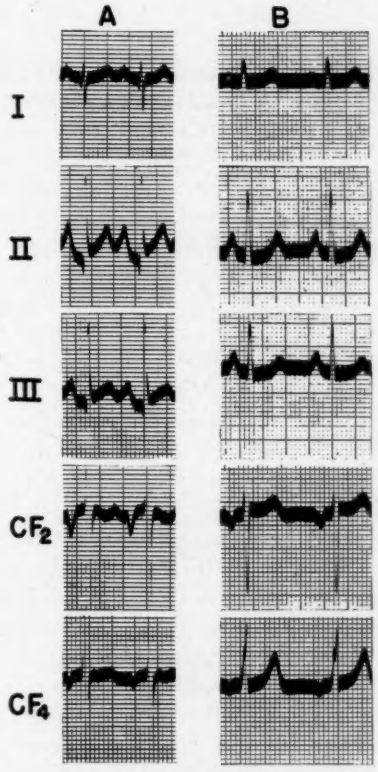

FIG. 3.—*A*, A case of congenital heart disease with right ventricular preponderance and P-pulmonale and its equivalent in CF_2. In this 19 year old male there was no evidence of pulmonary disease or abnormality. Discussed in text. *B*, A case of psychoneurosis without evidence of cardiac or pulmonary disease showing, besides S–T depression in Leads II and III and QRS almost entirely inverted in CF_2, the P-pulmonale pattern and its chest lead equivalents. Discussed in text.

auricular electrocardiogram must be attributed to some other factor. Perhaps Nordenfelt[23] is correct in his view that this P pattern occurs for some reason in individuals having a labile autonomic nervous system such as might occur in our group of mentally dis-

* The Editor is of the opinion that in addition to changes in position, cor pulmonale may be caused by any condition that raises right intra-auricular pressure sufficiently, whether primarily in the pulmonary artery, the lungs, the left auricle or even further "downstream." In experiments performed over 25 years ago[22] partial clamping of the pulmonary artery brought out this point.—EDITOR.

turbed patients. However, another factor, altered position of the heart, should also be considered. A study of routine tracings taken in the Heart Station on psychotic patients prior to shock therapy revealed that P-pulmonale is more common in patients with an asthenic habitus than in those of a sthenic build. This would seem to indicate that the asthenic habitus with the low diaphragm and centrally located heart is the important factor in imitating P-pulmonale, rather than any supposed abnormality of the autonomic nervous system.

The question follows as to what rôle an altered position of the auricles might play in the production of P-pulmonale in cases of chronic pulmonary disease. It may be seen in previously published articles[1,24,32,38] that changes in position from the recumbent to the sitting, particularly in young asthenic individuals with centrally placed hearts will produce alterations in the auricular complex similar to the P-pulmonale. These changes may be accompanied by a prominent S in Lead I, depressed S–T segment in Leads II and III, and an inverted T_2 and T_3, thus imitating in its entirety the pattern of chronic cor pulmonale.

The asthenic individual and the typical case of cor pulmonale, on fluoroscopic examination, both show a low diaphragm with an abnormal position of the auricles. Hence it is quite possible to attribute the P-pulmonale pattern to such an altered auricular position without necessarily assuming involvement of the auricular muscle. In chronic cor pulmonale, fluoroscopy often fails to reveal the right auricular enlargement which is expected with right auricular involvement.[5,27] This lends further support to the belief that this P pattern is due mainly to the abnormal position of the auricles associated with chronic pulmonary emphysema, pulmonary fibrosis, bronchiectasis, and other chronic lung affections.

The available postmortem studies regarding auricular involvement in chronic cor pulmonale[3,19,40] are equivocal, and further anatomic examinations from this point of view are necessary to estimate the rôle of position of the auricle in the P-pulmonale pattern. While these observations on auricular position as a cause of these P-wave changes show that this pattern may be found in cases without pulmonary disease, nevertheless, analyses reveal that the P-pulmonale is suggestive of chronic lung involvement if the asthenic build can be ruled out. The P-pulmonale pattern together with a right ventricular preponderance and/or "low voltage," represents the characteristic electrocardiogram of chronic cor pulmonale, although as evidenced by our series not all these characteristics are seen in every case.

Summary. 1. Fifty consecutive cases of P-pulmonale were studied in order to determine the significance of this P-wave pattern.

2. In 40 cases there was clinical and/or Roentgen ray evidence of chronic pulmonary disease as suggested by the auricular electro-

cardiogram. The 10 exceptions were 1 each of congenital heart disease, acute cor pulmonale, recent myocardial infarction, hyperthyroidism, and 6 cases with the diagnosis of psychosis, or psychoneurosis without cardiac or pulmonary involvement.

3. Eight cases of P-pulmonale with autopsy control were all found to have anatomic evidence of chronic pulmonary disease.

4. The P-pulmonale pattern occurs in individuals of asthenic habitus without evidence of cardiac or pulmonary involvement.

5. The characteristic P-pulmonale in the chest Leads CF_2 and CF_4 is an inverted P-wave of normal duration in cases showing P-pulmonale in the limb leads.

Conclusions. 1. The P-pulmonale pattern is not pathognomonic of chronic pulmonary disease, since it occurs in its absence, as it appears in a variety of other conditions.

2. P-pulmonale in association with low "voltage" in the limb leads or with right ventricular preponderance represents the characteristic electrocardiogram of chronic cor pulmonale.

3. It is of diagnostic importance to distinguish the P-pulmonale pattern from that seen in rheumatic mitral stenosis. The P-wave pattern can be used as a diagnostic hint in determining the cause of right ventricular preponderance if both are found in the same record.

4. Further anatomic and Roentgen ray correlation studies are necessary to establish definitely whether P-pulmonale is due to altered position, increased strain on, or hypertrophy of the right auricle.

We are indebted to the several physicians of the hospital staff for permission to report their cases, to Dr. O. Saphir of the Department of Pathology, for his necropsy report on the cases used in this study, and to Dr. L. N. Katz for his advice and suggestions in the preparation of this paper.

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"ESSENTIAL" HYPERTENSION. A CONCEPT OF ITS MECHANISM*

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RECENT studies have suggested that a substance can be obtained from renal tissue which is effective in lowering elevated blood pressure.[14,27] Because this material seems of therapeutic value there is need to reëxamine the problem of arterial hypertension, to define its nature and to appraise the various factors which contribute to its development.

Arterial hypertension is probably not the result of a single factor.[37] Although the blood pressure may become chronically elevated through mechanisms which are in most instances similar, the various influences which initiate these mechanisms are in all likelihood different. It is the purpose of this report to identify these influences so that they may be studied separately. It is also desirable that those which have been investigated experimentally be related to their clinical counterparts.

The experimental evidence points to the kidneys as having a

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causal relation to the condition. While there are occasional cases in man resembling the non-renal hypertension of animals, in most instances the kidneys likewise seem to be involved in some manner, directly or indirectly. This discussion will deal, therefore, with concepts based on this hypothesis and will assume that *renal ischemia*[10] constitutes the occasion for the existence of hypertension and initiates its development in most circumstances.

It is necessary that the phrase "renal ischemia" be defined. As used in this discussion it has the meaning given to it by Goldblatt,[10] implying less arterial blood in the kidneys due to an increase in resistance to the flow of blood through the kidneys. When a renal artery is partially constricted, or the lumina of the afferent arterioles narrowed, blood flow depends upon: 1, the degree of constriction; and, 2, the systemic blood pressure, as long as other factors (viscosity of blood, cardiac output, blood volume) remain constant. If No. 1 causes an increase in No. 2, and No. 2 becomes elevated enough to overcome the increased resistance caused by No. 1, the kidney will no longer be ischemic. If then the factors giving rise to the constriction remain unchanged, the kidney retains the capacity for becoming ischemic should the blood pressure fall. If the constriction is great enough to overcome increased blood flow caused by a rise in blood pressure, the kidney will remain ischemic, although less than if blood pressure were unchanged. Renal ischemia, by actual measurement therefore, may or may not be present when the blood pressure is elevated, even though the conditions giving rise to it continue to act. Narrowing of the efferent arterioles, which causes ischemia of the tubular vessels, may also result in diminution of total blood flow.

The influences which are at work in arterial hypertension include: A, a *Constitutional Factor*, an unknown defect suggested by the frequent presence of similar cases in the family histories of patients; B, the *Causes of Renal Ischemia*, such as are known in man and in animals; C, the *Mechanism of Hypertension*, as suggested by the available evidence; and, D, the *Effect of Elevated Blood Pressure*, as seen by clinical and pathologic examination. To simplify discussion, these elements have been arranged in Figure 1.

A. The Constitutional Component of Arterial Hypertension. Certain findings suggest that individual susceptibility is an important factor in causation. First, the condition appears to be hereditary in a large percentage of cases,[15] since arterial hypertension is present in the families of most patients exhibiting it. The children of hypertensive parents often react in an exaggerated fashion to tests of vascular irritability, even when their blood pressures are normal.[16] Those who do are, in fact, more liable to develop hypertension later in life than are others who react normally.[17]

Second, individuals exhibiting "early" or "mild" arterial hypertension are for the most part of the "nervous type."[32] They are

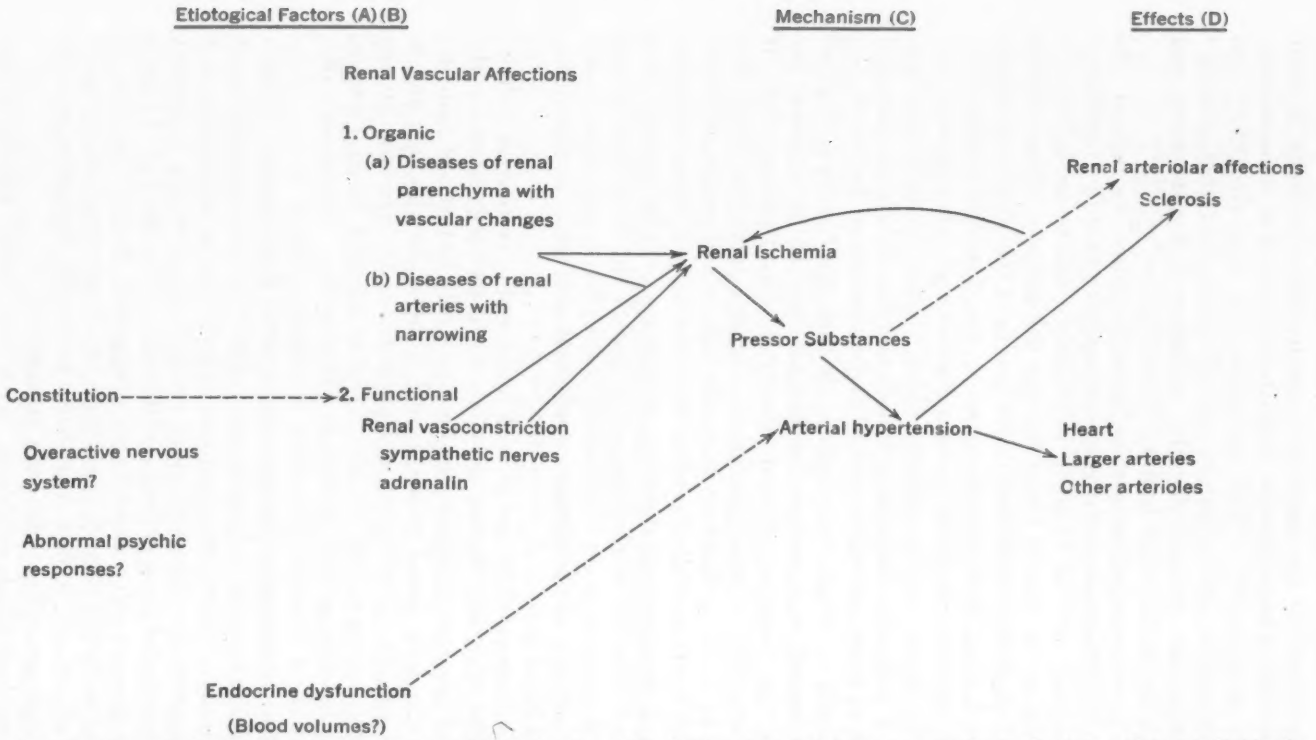

FIG. 1.—A concept of the mechanism of arterial hypertension. The letters *A* to *D* refer to paragraphs in the text. Taken individually those arrows marked by a solid line represent influences which have been demonstrated in experiments or by other good evidence; those marked by a dotted line are less well understood. Briefly, in predisposed individuals renal ischemia can be caused by intermittent functional renal vasoconstriction, by this in conjunction with organic narrowing of the renal vascular system, or (rarely) by the latter acting alone. The resulting hypertension causes organic changes in the renal arterioles which continue the existence of ischemia and hypertension.

either obviously high-strung, emotional, excitable people, or they admit the occurrence of great internal excitement which they manage to keep under control. Their responses to ordinary emotional stimuli are often excessive.

Third, organic renal diseases seem to cause hypertension in certain individuals[20,28,38] and not in others. These facts suggest that some persons are more susceptible.

The "constitutional component" means, therefore, a defect in certain individuals which predisposes them to arterial hypertension. This defect may be hereditary, or the result of early environmental influences. Its obvious clinical manifestations refer to the nervous system, especially to those structures having to do with emotional reactions and their effects upon blood-vessels. That the sympathetic nervous system may exert a pronounced effect upon the blood-vessels of the kidneys is discussed elsewhere.

Animals also exhibit different degrees of susceptibility. In most dogs, *both* renal arteries must be constricted in order to induce chronic hypertension,[10] although occasionally they develop it after constriction of only one. (This applies particularly to excitable, nervous dogs. Three such animals in this laboratory exhibited arterial hypertension for 18 months after 1 kidney was treated.) Rats, on the other hand, are affected by injury to 1 kidney,[46*] developing cardiac hypertrophy and hypertension[33,36] often with renal arteriolar necrosis.

B. The Causes of Renal Ischemia. 1. ISCHEMIA DUE TO ORGANIC VASCULAR CHANGES. (*a*) *Diseases of the Smaller Blood-vessels.* In *man* the persistence of hydronephrosis results in marked diminution of the vascular supply of the kidney and so probably leads to renal ischemia.[7] It is probable that chronic atrophic pyelonephritis also results in ischemia, scarring of the parenchyma after infection has healed producing lesions of blood-vessels resulting in reduction of blood flow.[6,45] The effects of renal infections upon blood flow have been little studied. Lesions resulting from chronic glomerulonephritis found postmortem suggest, from the pathologic viewpoint, that renal ischemia may have been present. Renal ptosis may be accompanied by ischemia.[21] Trauma results in a similar change especially if scarring follows. Other renal diseases may produce similar effects.

In *animals* obstruction to the flow of urine during brief experiments results in renal ischemia;[8] in rabbits, profound vascular changes accompany protracted experiments.[18] Many other affections of the kidneys experimentally produced can be regarded as resulting in ischemia.

Arterial hypertension is often associated with renal affections in *man:* with pyelonephritis,[45] nephroptosis,[21] prostate obstruction,[24]

* Attempts to produce hypertension by causing unilateral hydronephrosis, while successful in rats, failed in dogs.

hydronephrosis, and many other abnormalities of the kidneys.[20,28,38] Indeed, certain individuals develop elevated blood pressures as an early accompaniment of Bright's disease resembling cases of "essential hypertension."[9]

In *animals* arterial hypertension accompanies many of these conditions when they are experimentally produced. In rats it occurs with considerable frequency when one kidney is affected by perinephritis induced by cellophane,[25] traumatic injury and hydronephrosis.[33,36] In rabbits and dogs other renal affections, probably resulting in ischemia, appear also to cause it.

It is not certain whether a single lesion of the renal arterioles, arteriolar sclerosis, causes or results from arterial hypertension in man. Because the evidence in animals suggests, however, that it follows elevation of blood pressure, it is in this case regarded as an *effect* of the disease. This relation is discussed elsewhere.

(*b*) *Diseases of the Larger Arteries.* Narrowing of the mouths of the renal arteries by arteriosclerotic changes appears to reduce renal blood flow in a manner analogous to the principle of the Goldblatt clamp, as does narrowing of their lumina at their bifurcation, or in their intrarenal branches. The degree of ischemia, and the amount of renal tissue which is ischemic depends, of course, upon the location and extent of the lesion. Other more unusual affections of the arteries supplying the kidneys also cause ischemia, such as progressive thrombosis of the aorta, periarteritis nodosa, and perhaps coarctation of the aorta.

In animals, partial constriction of the renal artery obviously causes renal ischemia.[10] Partial constriction of the aorta above the mouths of the renal arteries brings about the same result.[31,43] These procedures lead to general vaso-constriction and arterial hypertension and to a change in intrarenal hemodynamics constricting the efferent arterioles.[5]

Arterial hypertension has been related to renal arteriosclerosis,[1] to periarteritis nodosa and to coarctation of the aorta.[31,43] All are believed to be dependent on ischemia.

2. Ischemia Due to Functional Disturbances. Injection of adrenalin into *human beings* results in prolonged renal vasoconstriction more especially of the efferent arterioles.[40] Psychic stimulation (anxiety) also can apparently produce renal ischemia.[40] This effect is achieved either through the liberation of adrenalin or through activity of the renal vasoconstrictor nerves of the sympathetic nervous system.

In *animals*, injection of adrenalin produces renal ischemia, the efferent arterioles being affected by small doses and the afferent also by larger ones.[30] Stimulation of the renal sympathetic nerves causes the same effect.[3]

Prolonged arterial hypertension has not been produced experimentally by either of these means. In rats the injection of single

large doses of adrenalin leads to cardiac hypertrophy.[33,36] Transient hypertension (4 to 6 weeks) may follow the injection of adrenalin in oil in dogs with normal blood pressures when one kidney is ischemic.[44]

In *human beings*, the sympathetic nerves supplying the splanchnic area are extremely important in maintaining an elevated blood pressure. When all of them are cut by means of preganglionic resection[41] (thus effectively denervating the kidneys), arterial hypertension and its effects disappear in a large proportion of cases. Because renal blood flow is not always reduced by this procedure, but sometimes increases,[42] these nerves probably exert an adverse influence upon it, contributing to hypertension by the results of their action. The possibility, therefore, exists that repeated psychic stimulation in predisposed individuals, by affecting the renal sympathetic nerves, results in enough renal ischemia to cause hypertension. If stimulation continues long enough, hypertension would become permanent from the establishment of changes in the renal arterioles.

3. The Relation Between Organic and Functional Renal Ischemia. In anesthetized dogs when ischemia results from partial constriction of the renal artery, it is profoundly influenced by the injection of adrenalin.[39] Moderate reduction in renal blood flow of short duration results from large doses if the kidney is normal; if a mechanical clamp has been applied to a renal artery and blood flow has already been reduced, minute doses produce greater effects lasting much longer. When the kidney is already ischemic the action therefore is markedly increased.

Arterial hypertension may result, furthermore, from the summation of these two actions (adrenalin and constriction), although neither of them alone has had much effect. Chromaffin tissue or the sympathetic nervous system may, therefore, play a part in the production and maintenance of hypertension by the Goldblatt method. This possibility has not been investigated in man.

C. The Mechanism of Hypertension Due to Renal Ischemia. When kidneys are ischemic, pressor substances enter the general circulation. These act on the smooth muscle of arterioles, increase peripheral resistance and, therefore, raise blood pressure. The nature of this material and the manner of its coming into existence is uncertain.

There are two principal theories: Page[26] believes that renin is released by kidneys when their pulse pressure is reduced. Renin, he thinks, then acts upon a pseudo-globulin in the blood to form "angiotonin," which has been isolated and identified as a pressor substance. It is the action upon arterioles of angiotonin, or products arising from it, that causes hypertension. As a variant, another group of investigators[23] regards renin as an enzyme, which acts upon its globulin substrate to form a pressor substance "hypertensin"

(identical with "angiotonin"). Another enzyme, "hypertensinase," present in blood and tissues, destroys it.

The second view is that of Holtz.[19] Kidneys contain the enzymes decarboxylase and amine oxidase, the latter acting only in the presence of oxygen. When the supply of oxygen is reduced (*i. e.*, during ischemia), decarboxylation of certain amino acids continues, but deamination is incomplete. The partial interruption of the metabolism of these amino acids results in the formation of amines, many of which are pressor substances. The most powerful are phenolic compounds.* Amine oxidase has a certain specificity; it catalyzes the oxidation only of compounds having an amino group on the end of a side chain,[2] and does not affect diamines. Its action is much greater on amines containing a phenolic nucleus (tyramine and its derivatives, indolethylamine).

D. The Effects of Hypertension on the Vascular System. Chronic arterial hypertension produces certain effects on the heart, blood-vessels and kidneys. The heart becomes enlarged and the wall of the left ventricle thickened. This change is greater when the coronary arteries are affected.

When the level of blood pressure is very high (in younger individuals), or when general arteriosclerosis accompanies hypertension, arteries may rupture. The consequences are important if the ruptured vessel is in the brain. In other localities less serious disturbances result.

The nature of the effect of arterial hypertension on the vessels of the kidneys is less clear. Sclerosis of the afferent arterioles is an almost universal accompaniment of chronically elevated blood pressure.[22] Constriction of the efferent arterioles, and of course renal ischemia, is present in most cases.[11]† It is not yet certain whether arteriolar sclerosis comes first and then ischemia and hypertension, or hypertension causes changes in the arterioles which then serve to make permanent narrowing of the renal vascular bed.

There is some evidence for the relation of these occurrences in experiments. In rats, when hypertension results from injury to one kidney, arteriolar sclerosis (and necrosis) are found in the other.[33,36,46] Dogs develop these lesions in organs other than the kidneys when bilateral renal ischemia is marked.[10] In human beings exhibiting one diseased kidney, nephrectomy reduces blood pressure when renal vascular disease is not advanced.[35] These observations suggest that renal arteriolar sclerosis accompanies hypertension,

* Because angiotonin is inactivated by tyrosinase[34] it is probably a phenolic compound.

† It is interesting in this connection that the efferent arterioles are constricted by many of the influences believed to be implicated in arterial hypertension; adrenalin and related compounds, renin and angiotonin, the action of the sympathetic nervous system. A situation exists in the kidneys, therefore, which may not only cause hypertension, but also be an effect of it.

and is one of its effects. The lesions then prevent the reëstablishment of normal blood flow.

Endocrine Dysfunction and Hypertension. The nature of what has been called "endocrine" hypertension is less clear. In rats, Byrom[4] produced in the livers and kidneys vascular lesions similar to those seen in eclampsia, by injecting pitressin after previous administration of female sex hormone. Griffith[12] has induced arterial hypertension in them by the use of posterior pituitary extract and water. He has also suggested that hypertension may result from retention of water and increase in the circulating volume of blood.[13]

In *human beings*, some hypertensive individuals have in their plasma antidiuretic substance; a few have been improved by irradiation of the pituitary gland with Roentgen ray.[29] Fall in the level of blood pressure along with disappearance of the antidiuretic substance suggests a relation between them.

The association of some cases with endocrine diseases is well established. If endocrine dysfunction is the initiating factor, the maintenance of the disease may be dependent on secondary renal arteriolar changes.

Recapitulation. Arterial hypertension, according to this idea, is therefore a state characterized by increased peripheral resistance owing to the presence of circulating pressor substances in the blood. These substances are released by ischemic kidneys and may be of several varieties.[47] They cause changes in arterioles, and in the hemodynamics of the kidneys, leading to arteriolar affections. A "vicious circle" is therefore established: renal ischemia giving rise to hypertension, which results in renal arteriolar sclerosis and the maintenance of ischemia (and hypertension).

Two conditions which occasion renal ischemia, therefore, initiate this "vicious circle:" 1, functional (spasmodic) constriction of arterioles by nervous or hormonal influences; and 2, structural (organic) changes in the renal blood-vessels. A third condition, also a structural change (renal arteriolar sclerosis) arises as a result of hypertension, acting in such a way as to continue the existence of renal ischemia. The first is probably active in most cases of hypertension,* varying considerably in degree in different individuals, but capable of initiating it alone under the proper circumstances. When organic renal ischemia is already present, hypertension may result from slight intermittent increase in renal vasoconstrictor tone. When the kidneys are otherwise normal, the activity of the sympathetic nerves must be comparatively greater, and their action called into play repeatedly in order to initiate the sequence of events leading to chronic hypertension.

Discussion. The view here presented makes clear some of the variations of the disease arterial hypertension. It usually depends upon two factors (rarely one) which cause a third, a similar one, to

* This may not be true for the hypertension associated with renal insufficiency.

come into being. Obviously the rate of progress of the condition resulting from these factors is determined by the relative parts which each play.

If the functional element acts alone, the course of the disease is prolonged (benign), depending for the most part upon the degree and frequency of action of the renal vaso-constrictor nerves, and those factors which influence them. Patients exhibiting symptoms predominantly of nervous origin vary, therefore, in their courses from long-standing "mild" hypertension, to a severe disease characterized by a labile blood pressure easily influenced by rest and sedatives. Rarely does the course become "malignant."[37]

If the structural element is progressive, and the functional one continues to exert its influence, the course of the disease is more rapid and death results from renal insufficiency.[38] On the other hand, if the structural element is stationary or only slowly progressive (as in arteriosclerosis), the course depends upon the influence of the functional element. If both the functional and structural elements act with increasingly greater influence, a "malignant" course results. (Although, as some think, the so-called "malignant" hypertension may be a distinct disease with a distinct pathologic anatomy, as indicated by the term, necrotizing arteriolitis, on clinical grounds it often appears to be a terminal stage of chronic arterial hypertension.) Other cardiovascular conditions also affect the outcome.

Procedures designed to alter these influences, and therefore the disease itself, naturally fall into three classes. A. The functional (spasmodic) factor can be changed by removing those environmental influences which cause constriction of the renal blood-vessels, by the administration of sedatives to lessen their effects, by the reëducation of the individual so that he no longer reacts to them, and by the surgical interruption of the effector pathways of the sympathetic nerves supplying the kidneys. B. The structural (organic) factor can be altered by the removal, for example, of a diseased, ischemic kidney, by attempting to influence degenerative vascular affections of the kidneys, or by increasing renal blood supply through surgical methods. C. The pressor substances responsible for hypertension can perhaps be destroyed by some of the newer extracts, thereby preventing the *effects* of the disease from progressing. Obviously the value of any of these methods depends for the most part upon the degree of secondary arteriolar sclerosis present in kidneys subjected to long-standing arterial hypertension.

Summary. A way of thinking about arterial hypertension has been presented, which takes into account the possible rôle of renal ischemia and those factors which cause it.

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BOOK REVIEWS AND NOTICES

CLINICS. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Successor to *The New International Clinics*. Philadelphia, J. B. Lippincott Company. Bi-monthly publication. Price, $12.00 a year.

After 4 years, *The New International Clinics* has given way to the present journal, which aims to acquire flexibility by selecting material on the basis of its practical significance, rather than as coming from special institutions or localities. The new journal will appear every 2 months, supplemented by original articles, brief "clinics," and occasional Reviews of recent progress. The Editorial Board shows but little change, the retention of Dr. John W. McNee and Dr. Jonathan C. Meakins preserving its international character. The first number is a symposium on Burns and Shock, and includes 6 articles. E. K.

PHARMACOPŒIA OF THE UNITED STATES OF AMERICA. Twelfth Revision. By authority of the U. S. Pharmacopœial Convention meeting at Washington, D. C., 1940. Prepared by the Committee of Revision and Published by the Board of Trustees. Pp. 880. Easton, Pa.: Mack Printing Company, 1942. Price, $7.50.

OUR Pharmacopœia needs no recommendation. The modifications of this 12th decennial revision and of future plans are best seen in the following quotations from the Preface:

"Certain basic policies were written into the first Pharmacopœia in 1820, and the Twelfth Revision marks a new era in its growth and development. For the first time a program is fully launched for a new Pharmacopœia every five years, a bound 'supplement' halfway between, and, to meet the frequently occurring situations which require immediate attention, 'Interim Revision Announcements' or sheet 'Supplements,' whenever these are required. By these accelerated procedures the Pharmacopœia is endeavoring to keep pace with the rapid developments of modern medicine and the related sciences. . . . .

"Dr. Lyman Spalding, the founder and Chairman of the first United States Pharmacopœia, stated 'It is the object of a Pharmacopœia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood.' Advisory boards and committees have been authorized for collaboration in the standardization of many U.S.P. products. These items include the vitamins, antianemia preparation, sterile products for parenteral use and for the needs of surgery, blood substitutes, glass container standardization, the assay of digitalis, ergot, parathyroid, epinephrine, insulin, adrenal cortical extract, the sex hormones, and numerous other substances and tests. . . . .

"Since the publication of the U.S.P. XI, the revised Federal Food, Drug, and Cosmetic Act of 1938 has been enacted by Congress, and the Pharmacopœia of the U. S. is recognized as one of the 'official compendia.' The officials of the Canadian Government have collaborated in the preparation of some of the U.S.P. standards. There has also been close co-operation between the British Pharmacopœial Commission and the Committee of Revision of the U.S.P. The co-operation of the U.S.P. Auxiliary Commissions of Cuba and Puerto Rico and the Pan American Sanitary Bureau officials at Washington and also the U.S.P. Auxiliary Commission of the Philippines has materially assisted in extending the information carried by the U.S.P. into many other associated countries. . . . .

"To assist in extending information both to physicians and pharmacists concerning the scope, therapeutic value, and use of pharmacopœial drugs and preparations, 48 articles were prepared under the supervision of a special Committee of the Pharmacopœia and officers of the American Medical Association. The authors of these articles were selected because of their special knowledge of and experience in the medical problem under consideration. . . . ."

Our Therapeutic Progress department contains two valuable discussions of the Revision (May, 1942 and this number).

SYNOPSIS OF ANO-RECTAL DISEASES. By LOUIS J. HIRSCHMAN, Professor of Proctology, Wayne University. Second Edition. Pp. 315; 182 illustrations and 12 color plates. St. Louis: C. V. Mosby Company, 1942. Price, $4.50.

THE Synopsis has been revised and some new material added. The local use of sulfanilamide is recommended in connection with some of the surgical procedures. A chapter has been added on Focal Infection of Ano-rectal Origin in which it is suggested that certain patients be desensitized to selected bacteria recovered from the anal crypts by hypodermic injections of 2 to 25 organisms at intervals of 5 to 7 days. Lymphopathia venereum is not indexed. The volume should be of value to the many readers who found the first edition useful. J. R.

THE RECEPTION OF WILLIAM BEAUMONT'S DISCOVERY IN EUROPE. By GEORGE ROSEN, M.D. Foreword by JOHN F. FULTON, M.D. Pp. 97; frontispiece of William Beaumont. New York: Schuman's, 1941. Price, $5.00.

BEAUMONT'S famous observations on the digestive activities of St. Martin's exposed stomach and his equally famous book—destined in Claude Bernard's words, "to produce an epochmaking effect in the history of digestion"—are properly cherished by the present generation as one of the greatest glories of American medicine. The little book is a bibliophile's *rarissima*, only recently reprinted again, and the man has been honored repeatedly with biographies, medals, shrines and lectureships. Little attempt seems to have been made, however, to trace the recognition of the book and of Beaumont's achievement in the century that has since elapsed.

This carefully prepared study by Dr. Rosen satisfactorily fills the gap. Even ardent Beaumontophils may be surprised to learn of the quickly favorable response abroad: the German, English and French articles, for instance, that appeared even before the publication of the "Experiments & Observations" in 1833; the prompt and favorable discussions of the new book in 1834 and 1835; foreign editions and translations; recognition by Claude Bernard and Carl Ludwig. Equally surprising is "the fact that during the last 40 years of the century Beaumont's researches are only mentioned three times," attributed by Dr. Rosen to Kussmaul's introduction of the stomach pump in 1867, and to greater emphasis on the chemical aspects of digestion.

Among items that might be objected to, though they are to be sure insignificant in evaluating the booklet, are: the many "incomplete" references, the omission of J. R. Young's "Experimental Inquiry" in the chapter on "Gastric Physiology before Beaumont" and Dr. Fulton's foreword limitation of Americans who profoundly influenced European medical thought before 1900 to Beaumont, Franklin and Weir Mitchell. Granted the flexibility of "profoundly," many would feel that Long and Morton, McDowell and Marion Sims, Gorgas, John Shaw Billings, and perhaps still others, might well be admitted to this august company. E. K.

HISTORY OF THE SCHOOL OF NURSING OF THE PRESBYTERIAN HOSPITAL. By ELEANOR LEE, A.B., R.N., Assistant Professor of Nursing, Department of Nursing, College of Physicians and Surgeons, Columbia University. Pp. 286; 58 illustrations. New York: G. P. Putnam's Sons, 1942. Price, $3.50.

THIS book covers far more than its title indicates, as one is very soon aware on reading this fascinating account of the development of this School of Nursing.

In the background one sees the picture of the community that New York was in 1892 with its poor that provided the need out of which grew a service built up by men and women from the citizens, who were socially minded, as well as those devoted members of the medical and nursing fields without whose loyal and constant attention such a fine institution could not have occurred.

With letters, pictures and diaries one gets a most intimate impression of how the present organization came about. It represents what was happening in many places throughout the whole country, a gradually emerging social conscience, an awakening to the needs of the underprivileged and of the responsibility of those in possession of scientific knowledge to meet those needs.

One might take as a prediction of the future social importance of nursing, the last sentence in the Appendix, which reads: "The nurse of this era who keeps pace with the advance of science will have undreamed-of opportunities to contribute to the betterment of the mental and physical health of mankind."

This book should be interesting to all who are engaged in the medical professions or who are aiding in any way the progress of this great work.

M. S.

DR. BARD OF HYDE PARK. By J. BRETT LANGSTAFF. With an Introduction by NICHOLAS MURRAY BUTLER. Pp. 365; 12 illustrations. New York: E. P. Dutton & Co., 1942. Price, $3.75.

DR. SAMUEL BARD is the famous physician who saved George Washington's life, when shortly after his inauguration Dr. Bard removed an anthrax carbuncle on his thigh. Dr. Bard was a founder of the Medical School in King's College, now the famous College of Physicians and Surgeons of Columbia University. These, perhaps may be counted as the most noted of his achievements, for the great works of man live after him. But they were only a part of the rich and full life of this remarkable man.

It is evident from the very beginning of the book that the author has spent many years in careful research on his subject. The reader may feel at times as if the research was the more important part of the biography, yet the vigorous personalities of Dr. Samuel Bard and of his father, Dr. John Bard, hurdle the dry facts which might otherwise weigh them down. Both father and son lived well into their 70's—one cannot write of the son without talking of the father, for each was so close to the other—and their lives were rich, full and vigorous to the end.

Dr. John Bard, the father, inherited from his wife's side of the family the Hyde Park property that is now the site of the home of our present President. Thus are linked the doughty characters of Revolutionary times with our present day historical figures, and dead names become living people.

This book presents, as fully as is possible in a popular biography, the complete and interesting life of Dr. Samuel Bard and also a small part of the Bard family background. As Samuel was an American of the third generation, his grandfather having come to America because of Huguenot persecutions in France, a feeling of liberty and sympathy for all people

predestined the character of Samuel Bard. His untiring search to relieve pain was the most natural of careers that he could follow, for the father Dr. John Bard, did much to crystallize his son's ideals. How well these foundations were laid is evidenced by the fact that Ducachet, his colleague, said: "There never was a medical man in the City of New York so universally known, so much beloved and esteemed as a practitioner. Indeed, so astonishingly popular was he at one time that notwithstanding the number of worthies who flourished contemporaneously in the same city, he was called to almost every person who was taken sick." E. F.

CLINICAL CARDIOLOGY. By WILLIAM DRESSLER, M.D., Attending Cardiologist, Israel Zion Hospital; Assistant Attending Physician, Brooklyn Hospital, New York. Pp. 692; 108 illustrations. New York and London: Paul B. Hoeber, Inc., 1942.

THE author states that the aim of this volume is to offer a practical guide to those who wish to engage in the study of heart disease and that particular emphasis has been placed on the use of inspection, palpation, percussion and auscultation. The entire field of clinical cardiology, including hypertension, is discussed. There are brief chapters on electrocardiography and roentgenologic examination. The book is concluded by a list of 294 statements, covering nearly 40 pages, entitled "Important Points to Remember."

After comparing this book with 4 of its recently published competitors in the same field, this Reviewer is unable to rank the present volume high in the group despite the fact that it contains much of the same orthodox material found in the others. Occasionally major errors are found, such as the statement to the effect that the intervals between all three sounds in gallop rhythm are practically equal. It is interesting that the author's conception of electrical potential is such that he can speak of potential differences having various directions. Opinions, some of which do not seem to be supported by the weight of available evidence, are at times stated so dogmatically in this book that the uninitiated would have no reason to suspect that they are opinions. Finally a statement that ". . . . it has become almost a routine procedure to prescribe digitalis whenever a heart disease, or merely an innocent murmur has been detected" suggests that the author has a much worse opinion of the standards of American practitioners than some who have worked with them for a much longer time. The book is not recommended. C. W.

QUESTIONS IN LABORATORY METHODS. By R. B. H. GRADWOHL, M.D., Director of the Graduate School of Laboratory Technique, St. Louis, Mo. Second Edition. Pp. 71. St. Louis, Mo.: The Gradwohl School of Laboratory Technique, 1942. Price, $2.50.

THIS is a well-printed 71-page booklet bound with spiral wire and heavy paper cover, measuring approximately 8 x 11 x ¼ inches. It is a compilation of "questions . . . . taken from examination papers . . . . accumulated over a period of 25 years" sorted as follows: The Microscope (255 questions), Metric System (86), Clinical Microscopy (318), Hematology (1647), Bacteriology (1589), Serology (117), Clinical Chemistry (275), Parasitology (204), Histological Technique (163), Basal Metabolism (45), Special Tests (191), and Miscellaneous Medical Subjects (345); a total of 5235 questions. This is the only publication of its kind in this field at present so far as the Reviewer is aware.

There are many questions in every section which, in the opinion of the

Reviewer, should not be put to laboratory technicians. These deal with diagnostic implications of laboratory findings, and are outside the proper province of the technician. They might be helpful to the physician preparing for special examinations. D. B.

PSYCHOSURGERY. By WALTER FREEMAN, M.D., PH.D., and JAMES W. WATTS, M.D., with THELMA HUNT, M.D., PH.D. Pp. 337; 81 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, $6.00.

FREEMAN and Watts, who have pioneered in the neurosurgical treatment in Psychiatry, have prepared a valuable survey of the history, the neuroanatomy, the physiology and the technique of prefrontal lobotomy and have reviewed the results of their own operations in psychotic patients and the available literature and presented it in a well-organized and scientific evaluation.

In Part II, entitled "The Frontal Lobes," the historical concepts, anthropology, topographic anatomy, the connections and functions of the frontal lobes are all adequately reviewed and material derived from experimental animals, the symptoms of frontal lobe tumors, frontal lobe atrophy, softenings and injuries and the results of frontal lobotomy in man are reviewed and evaluated in relation to the therapeutic surgical procedure.

Part III relates to clinical observations of prefrontal lobotomy and describes the improvements made by Freeman and Watts on the original Moniz technique.

There is a chapter devoted to the functions of the frontal lobes, a chapter on Mental Mechanisms and the Frontal Lobes which the critical reader will evaluate (as Drs. Freeman and Watts suggest) according to his own judgment. Some of the alterations in the mental functions reported and discussed are: 1, Reduced capacity of an individual to project himself into the future. 2, Restraint is somewhat impaired. 3, Reduced self-critical and self-absorptive capacity. 4, More extraverted, freer conduct. 5, Vivid but superficial emotional responses. 6, Delusional ideas may be retained but unpleasant emotional reaction to them is absent. 7, Impaired foresight.

The postoperative reëducation and rehabilitation of patients subjected to frontal lobotomy are of the utmost importance. Possibly this phase of treatment could be emphasized and outlined in greater detail in the book. Freeman and Watts have been very frank in assaying the positive and negative elements in frontal lobotomy and give a very fair statement as to the immediate as well as the ultimate risks. The operation is a drastic, last resort method and should be used only in those long-standing cases which fail to respond to other methods. Probably like other drastic treatment methods in Psychiatry, its development and application were stimulated by the demand for more direct treatment of the large static segment of the psychoses. It must be understood that recovery cannot be anticipated in patients subjected to frontal lobotomy. While one of the remarkable features of the operation is lack of apparent intellectual defect, it must not be stated that some defect of intellectual-emotional functions do not result. Throughout the book there is a frank approach to the question of accomplishment by the operation and there is no dodging of the issue regarding the unfavorable consequences.

The book is factual, well written, profusely illustrated with well-chosen photographs and drawings and charts. The psychiatrist will find the text fascinating, a valuable addition to his library and the neurosurgeon will be accurately informed as to technical detail. The volume offers an extension of knowledge for the psychologist, sociologist and every student of human emotion and conduct. H. P.

THE CARE OF THE AGED (GERIATRICS). By MALFORD W. THEWLIS, M.D., Attending Specialist, General Medicine, U. S. Public Health Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I.; Special Consultant, Rhode Island Department of Public Health. Fourth Edition. Pp. 589; 50 illustrations. St. Louis, C. V. Mosby Company, 1942. Price, $7.00.

THE first edition of this work appeared in 1919, the third not until 1936. Because of the recent remarkable increases in the average duration of human life and the keener interest in the subject of geriatrics, a fourth edition is required after 6 years. The rôle to be played by the aged in our total war effort has also become an important matter, and still more so is the problem of those in whom old age can be deferred.

The need for books of this kind, then, is obvious. The ability to condense adequate information on the subject into less than 600 small pages is at once questioned, and perusal confirms the opinion that a book half as long again would be twice as valuable. The leukemias in 2 pages, the eye in 6 pages, the ear in 7, could hardly get adequate attention.

Nevertheless, the book is well worth while, and as each edition has been an improvement on its predecessor, let us hope that a greatly enlarged fifth edition will soon appear. E. K.

THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 26, No. 4, July, 1942. Symposium on Industrial Medicine. Pp. 1345. Philadelphia: W. B. Saunders Company, 1942.

CONTENTS: "The Physician in Industry," by Dr. Carl M. Peterson; Organization and Management of an Industrial Medical Service," by Dr. A. L. Brooks; "Physical Examination in Industry," by Dr. Grant L. Bird; "Workmen's Compensation and Medicine," by Dr. Raymond Hussey; "Tuberculosis as a Compensation Problem," by Dr. C. O. Sappington; "Nutrition in Industry," by Dr. William A. Sawyer; "A War-Survey of Industrial Psychiatry," by Dr. Lydia G. Giberson; "The Measurement of Sickness Among Industrial Workers," by Dr. William M. Gafafer; "Fatigue and War Production," by Dr. Robert H. Flinn; "Prevention of Ill Health in Industry," by Dr. John H. Foulger; "Methods Employed in the Appraisal and Control of Industrial Health Hazards," by J. J. Bloomfield; "Indoor Environmental Atmosphere and Its Control," by Dr. W. J. McConnell; "Protective Ointments and Industrial Cleansers," by Dr. Louis Schwartz; "Effects of High Pressures; Prevention and Treatment of Compressed Air Illness," by Dr. Albert R. Behnke, Jr.; "The Pneumoconioses," by Dr. L. U. Gardner; "Lead Absorption and Lead Poisoning," by Dr. Robert A. Kehoe; "The Toxic Properties of Selected Less Familiar Metals," by Drs. Carey P. McCord and John J. Prendergast; "Recent Progress in Aviation Medicine," by Dr. Benjamin F. Jones.

Seldom has a publication concerned with industrial medicine held so much practical information in such a small space, as does the "Symposium on Industrial Medicine." The field in this branch of medicine is as varied and wide as the industry which it serves, yet nearly all phases are represented with a precise brevity by physicians who are recognized authorities.

The book can be read in 6 hours by an alert student but it lends itself well to broken reading. The usefulness of the volume is not restricted to those specializing in industrial medicine, and it should prove of particular value to physicians in these crowded days, who are being asked to include medical work in industrial plants that have been created for or converted to war

products in the past few months. In many instances this work is just as new to the physician as the plant is to the managers and workers, and there should be an especial thanksgiving that the publishers have filled the need for a clear discussion of industrial medical problems at this time.

V. R.

THE SURGERY OF PANCREATIC TUMORS. By ALEXANDER BRUNSCHWIG, M.S., M.D., F.A.C.S., Professor of Surgery, University of Chicago. Pp. 421; 123 illustrations, 1 color plate. St. Louis: C. V. Mosby Company, 1942. Price, $7.50.

INTEREST in the surgery of the pancreas has greatly increased in recent years, due to the recognition of island adenomas as a cause of hyperinsulinism and to the development of successful methods of attacking carcinoma of the head of the pancreas. Dr. Brunschwig has been a pioneer in this work and his monograph is the most thorough and complete treatise that has appeared on the subject. It should be available to every surgeon who contemplates the removal of pancreatic tumors and its perusal by physicians generally should lead to a clearer recognition of the possibilities and limitations of pancreatic surgery.

J. R.

ELECTROTHERAPY AND LIGHT THERAPY with the Essentials of Hydrotherapy and Mechanotherapy. By RICHARD KOVÁCS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and West Side Hospitals. Pp. 735; 413 engravings and a color plate. Fourth Edition. Cloth. Philadelphia: Lea & Febiger, 1942. Price, $8.00.

SINCE this well-known work first appeared some 10 years ago the rapid progress in physical therapy and the great demand for the book have necessitated new editions of which the present one is the fourth.

As in the previous editions, so also in this one, the subject matter is well organized. It begins with the essential physics—avoiding formulas and complicated equations—of electrical and light energies. Then follow in succession detailed descriptions of the various devices for the production of these energies, their physical and physiologic effects, indications and contraindications, technique of administration and their possible dangers. One new feature of this edition is the incorporation of 3 rather sketchy chapters on hydrotherapy and mechanotherapy. Next there follows a description of the application of physical therapy in a great variety of diseases and disorders in the various branches of medicine. This latter part of the book has been considerably enlarged, covering nearly one-third (217 pages) of the text. Discussion of treatment by means of various electrical and light agents naturally predominates in this part of the book, but, as the author states, "the correlated or interchangeable use of other and often simpler physical measures have always been emphasized." Several electrodiagnostic charts and tables have been appended to the text. A well-selected bibliography appears at the end of each chapter.

The relation of electrodiagnosis to the newer electrophysiology has been further stressed and new chapters have been devoted to short wave diathermy. The electric shock therapy method in mental conditions has been thoroughly described and chapters on peripheral vascular disease, chronic arthritis, traumatic and skin conditions rewritten and amplified.

Like the earlier editions, this book is an authoritative, comprehensive exposition of electro and light therapy. In reading the text, one is impressed with the author's thorough knowledge of his subject and his ability

to present the material in a clear, instructive manner. Relatively little space has been given to the discussion of controversial matters and to theories of a purely academic interest, the volume having been devoted chiefly to the description of methods of established value and to the discussion of problems of practical importance. In its field this book is a standard work in which the admirable text of the previous editions has been amplified and revised to include the latest developments in the field. This work cannot be recommended too highly. J. N.

STANDARD NOMENCLATURE OF DISEASE AND STANDARD NOMENCLATURE OF OPERATIONS. Edited by EDWIN P. JORDAN, M.D. Third edition. Pp. 1022. Chicago: American Medical Association, 1942.

IT is hard to understand why this authoritative Standard Nomenclature of Disease has not come into more general use since its compilation in 1933 by a distinguished group of medical men under the auspices of the Commonwealth Fund. The present "completely revised" edition has been developed under new auspices with a new editor and editorial advisory board; but retains the same basic plan and arrangement. Based on the Dewey decimal system, a Topographical Classification (to three digits) presents the parts of the body in 11 main divisions. An Etiological Classication in 12 main divisions covers all known causes of disease. Thus, ankylosis of the knee (tuberculous) would be numbered 248—123.4 (2, muscular-skeletal system; 4, a joint; 8, knee—1, infection; 2, a lower organism; 3, tubercle bacillus; .4, the result—ankylosis).

The commoner diseases have been picked out in bold-face type, and a standard classification of operative procedures added. The Introduction and Instructions to Librarians aid the beginner to overcome rapidly the superficially formidable arrangement. Various small additions have been made and the new edition is more easily usable by the beginner. We intend to make regular use of the classification in our own work and are sure that such a course would be desirable in all hospitals and other centers concerned with scientific medicine. E. K.

DEMONSTRATION OF PHYSICAL SIGNS IN CLINICAL SURGERY. By HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hospital, London, etc. Eighth edition, revised. Pp. 336; 455 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, $7.00.

THIS book is designed primarily for medical students and house officers but it is well worth the consideration and time of many surgeons who have finished their training. It contains a concise review of the physical signs which may be elicited in various surgical conditions and emphasizes important points to be sought in the history in connection with them. The methods of eliciting these signs are well illustrated. Many of the plates are in color. The evaluation of their significance is helpful when given in terms of the author's own experience.

No two surgeons are likely to agree completely on the evaluation of physical signs and students of this book may subsequently revise the importance of certain signs in the light of their own experience. However, the value of the book lies in emphasizing physical signs which are not elicited as frequently as they should be, and in demonstration the great amount of information which can be obtained without resort to complicated and time-consuming laboratory procedures. J. R.

ARCHITECTURAL PRINCIPLES IN ARTHRODESIS. By G. F. ROWBOTHAM, B.Sc., F.R.C.S. Pp. 132; 144 figures. St. Louis: The Williams & Wilkins Company, 1942. Price, $7.50.

WELL done, indeed! This splendid treatise on the architectural principles in arthrodeses is a genuine contribution to bone surgery. The principles, so well developed, so carefully portrayed, are by no means restricted to arthrodeses alone, but apply to bone repair in general.

From the foreword by Harry Platt, to and including the last chapter, one is impressed with the deep thought and reflection given to the entire subject.

The indications for an arthrodesis are generally accepted and may be regarded as uniformly sound. The common causes of failure are enumerated and the mechanical basis for their occurrence clearly illustrates this. The basic requirements of the architectural principles, namely, "1. The graft should be placed with its long axis in compression rather than in tension; 2. The breadth of the graft should be placed in the position of maximum stress; 3. A joint should be locked by two grafts crossing each other in the shape of the letter X; 4. There should be adequate protection of the graft," form the basis of the laws of bone repair in general, and, this emphasis, alone, would justify the publication. J. M.

OCCUPATIONAL TUMORS AND ALLIED DISEASES. By W. C. HUEPER, M.D., Assistant Director and Principal Pathologist, Warner Institute for Therapeutic Research, New York City. Pp. 896; many illustrations, 3975 references. Springfield, Ill.: Charles C Thomas, 1942. Price, $8.00.

THE ever-increasing interest in the problem of cancer as well as in the diseases associated with modern industry give this book a twofold value. After an introductory chapter surveying the significance of exogenous factors in the production of carcinoma, the author devotes himself to a consideration of the various organ systems and the causes produced therein by chemical and physical agents. The diversity of these substances is matched only by the enormously varied industries in which they occur. The total number of cases attributed specifically to a certain chemical in a particular industry are frequently quite small and one is reminded of the early bacteriologists who ascribed a particular disease to any and every bacterium they found in the tissues. The author, however, has admittedly attempted to include all available data, and his extensive bibliography will enable the sceptic to refer to the original sources and decide for himself.

The medico-legal aspects of the problem are considered in a separate chapter, as well as in the discussion of the individual lesions. The comprehensive index and good format add to the value of the book. It should be of interest to students of cancer, public health, and general medicine. H. S.

FUNDAMENTALS OF ANESTHESIA, An Outline by the Subcommittee on Anesthesia of the National Research Council. Pp. 217; 72 illustrations. Chicago: American Medical Association Press, 1942. Price, $2.50.

THIS manual is primarily intended for the instruction of medical officers as anesthetists. It has, however, a much wider field of usefulness particularly in the present emergency, where the administration of depressant drugs and the care of patients with respiratory and circulatory depression will be often in the hands of the inexperienced.

Written by a group of leading United States anesthetists, the outline is up to date in its coverage of inhalation, intravenous, and regional anesthesia. It covers the use of orally administered narcotics, but in a necessarily dog-

matic form. Its chief importance, however, is found in its sections on the management of depressed states of the respiratory and circulatory systems, whether these be due to narcotics, shock, surgery, and so forth.

One can recommend this small volume unhesitatingly to medical students, interns and residents who may soon join the armed forces. It will also prove useful to older physicians who may be called as medical officers with combat troops and who have forgotten the special problems discussed above. For semi-trained anesthetists it will be a valuable guide in the acquisition of skill in the more complicated phases of technical anesthesia since both fundamental techniques and more advanced methods are covered.

R. D.

CABOT AND ADAMS PHYSICAL DIAGNOSIS. By F. DENNETTE ADAMS, M.D., Harvard Medical School, Massachusetts General Hospital. Thirteenth Edition. Pp. 888; 399 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, $5.00.

IT has been noted recently that doctors entering the armed forces have manifested an outstanding deficiency in their physical diagnostic skill. This may be a reflection of the progressive de-emphasis that this subject has received in our teaching institutions. Perhaps, then, this publication is timely in once again lucidly and systematically presenting the well-established principles of the bedside examination.

That this book is one of the foremost in its field is obvious since it is now in its 13th edition. The 12th edition was a thorough revision and enlargement of the previous text. This edition represents lesser changes. The sections on the mouth, back, pulse, classification of heart murmurs and coronary heart disease have been thoroughly reorganized. The newer ideas on shock are concisely summarized in the chapter on congestive failure by the addition of a section on inadequate cardiac output. The list of clinical entities discussed has been enlarged and minor changes have been introduced where deemed beneficial by the author. The author has drawn freely from the experiences of his colleagues at the Massachusetts General Hospital. These men constitute some of the most eminent physicians in American medicine. Needless to say, the factual material is well grounded.

As a text for beginners one criticism is suggested. Physical diagnosis is frequently introduced to the medical student as his first clinical subject. The discussion of clinical entities, as it occurs in this book, is inaccessible to the young student. Teachers of physical diagnosis recognize the inefficiency and fruitlessness of discussing clinical syndromes with the preclinical student in physical diagnosis classes. However, for the upper class student and the practising physician this book is highly recommended. It is a worthy addition to any doctor's library.

D. T.

GRAY'S ANATOMY. By HENRY GRAY, F.R.S., Late Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. Edited by WARREN H. LEWIS, B.S., M.D., Member, The Wistar Institute of Anatomy and Biology, Philadelphia. Twenty-fourth Edition. Pp. 1428; 1258 figures, mostly in colors. Philadelphia: Lea & Febiger, 1942. Price, $12.00.

THE latest edition of this time-proven classic presents a most thorough revision. In addition, the Editor has obtained the assistance of 6 well-known anatomists as his associates, representing a unique departure from previous editions. Although the arrangement of chapters and subject matter that have characterized the book for so many years remains un-

changed, the text has been revised, rewritten and augmented by the latest information. Many new illustrations are included. Thirty roentgenograms stress the important rôle of roentgenography in anatomy as well as in medicine and surgery. These have been introduced in the chapter on Surface and Topographical Anatomy. The book has grown in size by only 47 pages, but its value to the students has increased tremendously. Thus, this new edition of an old standby can only increase its well-deserved popularity. D. C.

THE DYNAMIC STATE OF BODY CONSTITUENTS. By RUDOLPH SCHOENHEIMER, Late Associate Professor of Biological Chemistry, Columbia University. Pp. 78. Cambridge: Harvard University Press, 1942. Price, $1.75.

THIS is a monograph embracing the three Harvard University 1941 Edward K. Dunham Lectures for the promotion of the medical sciences. They were presented by Dr. Hans T. Clarke following the sudden death of the author. It is of primary interest to biochemists and clinicians interested in these problems. These lectures develop "a concept of metabolic 'regeneration,' wherein the central idea is the continual release and uptake of chemical substances by tissues to and from a circulating metabolic 'pool.' Coincident with these cyclic processes there occur among the components of the pool multitudinous chemical reactions, of which only relatively few are concerned with elimination of waste products." R. B.

A TEXTBOOK OF NEURO-ANATOMY. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Third Edition. Pp. 518; 307 figures. Philadelphia: Lea & Febiger, 1942. Price, $6.00.

THIS book gives a reliable account of the parts of the nervous system and their interrelationships, rather than detailed descriptions of cellular structure. The chapter on the thalamus now includes a modern consideration of its functional relationships and a section on the hypothalamus. Many of the cuts are reproduced better than in previous editions. The authoritative chapter on the autonomic system still remains one of the best in the book. W. A.

CORRECTION.—The price of the *International Journal of Sex-Economy and Orgone-Research*, reviewed on page 290 of the August, 1942, issue was given as $5 a year—the correct price is $3.

NEW BOOKS

A Handbook of Allergy for Students and Practitioners. By WYNDHAM B. BLANTON, M.A., M.D., LITT.D., Professor of Clinical Medicine and Chief of the Immunology Clinic, O.P.D., Medical College of Virginia, Richmond, Va. Pp. 190; 20 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, $3.00.

Medical Progress Annual. Vol. III–1942. Edited by ROBERT N. NYE, M.D., Managing Editor of *The New England Journal of Medicine*. Pp. 678; several figures. Springfield, Ill.: Charles C Thomas, 1942. Price, $5.00.

A Short History of Cardiology. By JAMES B. HERRICK, M.D., Emeritus Professor of Medicine, Rush Medical College; Consulting Physician to Presbyterian Hospital, Chicago. Pp. 240; 48 plates. Springfield, Ill.: Charles C Thomas, 1942. Price, $3.50.

Professional Adjustments II. By GENE HARRISON, A.B., R.N., Educational Director, Druid City Hospital School of Nursing, Tuscaloosa, Ala. P. 424. St. Louis: C. V. Mosby Company, 1942. Price, $3.50.

Shock, Its Dynamics, Occurrence and Management. By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College, Philadelphia. Pp. 324; 36 engravings. Philadelphia: Lea & Febiger, 1942. Price, $4.50.

CENTRAL AUTONOMIC REGULATIONS IN HEALTH AND DISEASE. With Special Reference to the Hypothalamus. By HEYMEN R. MILLER, M.D., Associate Attending Physician, Montefiore Hospital, New York. Introduction by JOHN F. FULTON, M.D., M.A., D.PHIL. (OXON.), Sterling Professor of Physiology, Yale University. Pp. 430; 61 figures. New York: Grune & Stratton, 1942. Price, $5.50.

CASTOR OIL AND QUININE. Once a Doctor, Always a Doctor. By GEORGE WONSON VANDEGRIFT, M.D. Pp. 252. New York: E. P. Dutton & Co., Inc., 1942. Price, $3.00.

A Bibliography of Aviation Medicine. By EBBE CURTIS HOFF and JOHN FARQUHAR FULTON. Prepared for the Committee on Aviation Medicine, Division of Medical Sciences, National Research Council Acting for the Committee on Medical Research, Office of Scientific Research and Development, Washington, D. C. Pp. 237. Springfield, Ill.: Charles C Thomas, 1942. Price, $4.00.

Hospital Discharge Study. Vol. I: Hospitals and Hospital Patients in New York City. By NEVA R. DEARDORFF, PH.D., and MARTA FRAENKEL, M.D. Pp. 209; many tables. Welfare Council of New York City, 1942. Price, $1.00.

This analysis of 576,623 patients discharged from 113 of New York City's hospitals during the year 1933 is the first attempt at a complete study of morbidity of any large group of patients. The comprehensive data thus developed will be studied by all those interested in morbidity statistics. This work may well be the beginning of a new national morbidity code. R. B.

Outline of Histology. By MARGARET M. HOSKINS, PH.D., and GERRIT BEVELANDER, PH.D., Department of Anatomy, College of Dentistry and the Graduate School of Arts and Science, New York University. Pp. 286; many figures. St. Louis: C. V. Mosby Company, 1942. Price, $2.50.

In a striking modern loose-leaf binding, Hoskins and Bevelander have presented a concise outline of histology, profusely illustrated. Part I deals with general histology and Part II, about one third of the book, considers in detail dental histology and embryology. The excellent illustrations are mostly from original pencil sketches. They depict what the student could be expected to see through the microscope. Blank leaves are inserted with each chapter. W. A.

A Manual of Experimental Embryology. By VICTOR HAMBURGER, Washington University. Pp. 213; many figures. Chicago: The University of Chicago Press, 1942. Price, $2.50.

Introduction to Parasitology. By A. S. PEARSE, Professor of Zoölogy, Duke University. Pp. 357; 448 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, $3.75.

The Medical Clinics of North America. Vol. 26, No. 5 (Boston Number). Pp. 306; many figures. Philadelphia and London, W. B. Saunders Company, September, 1942. Price, $16.00 per year (cloth binding), $12.00 (paper binding), 6 vol. set.

Roentgen Treatment of Diseases of the Nervous System. By CORNELIUS G. DYKE, M.D., F.A.C.R., Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University; Director, Depart. of Radiology, Neurological Institute of New York, and LEO M. DAVIDOFF, M.D., F.A.C.S., Chief, Depart. of Surgery, Attending Neurological Surgeon, Jewish Hospital of Brooklyn. Pp. 189; 12 engravings, 7 charts, 16 graphs. Philadelphia: Lea & Febiger, 1942. Price, $3.25.

NEW EDITIONS

An Introduction to Materia Medica and Pharmacology. By HUGH ALISTER MCGUIGAN, PH.D., M.D., Professor of Materia Medica, Pharmacology and Therapeutics, University of Illinois College of Medicine, Chicago, and ELSIE E. KRUG, B.S., R. N., Science Instructor, St. Mary's School of Nursing, Rochester, Minn. Third Edition. Pp. 779; 47 text illustrations, 37 color plates. St. Louis: C. V. Mosby Company, 1942. Price, $3.50.

First Aid and Bandaging. By ARTHUR D. BELILIOS, M.B., B.S. (LOND.), D.P.H. (ENG.) and others. Fourth reprint. Pp. 628; 239 figures. Baltimore: Williams & Wilkins Company, 1942. Price, $1.75

War and the Doctor. Essays on the Immediate Treatment of War Wounds. Edited by J. M. MACKINTOSH, M.D., Chief Medical Officer of the Depart. of Health for Scotland. Second Edition, reprinted. Pp. 135. Baltimore: William Wood & Co., 1942. Price, $2.00.

A Curriculum for Schools of Medical Technology. By ISRAEL DAVIDSOHN, M.D., Director of Laboratories and Pathologist, Mt. Sinai Hospital, Chicago; Assistant Professor of Pathology, College of Medicine of the University of Illinois. Second Edition. Pp. 47. Muncie, Ind.: Published by Registry of Medical Technologist, Ball Memorial Hospital.

Human Pathology. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio. Sixth Edition. Pp. 817; 460 illustrations and 16 color plates. Philadelphia: J. B. Lippincott Company, 1942. Price, $10.00.

This new edition of Karsner presents a thorough revision of an excellent text. The format has been changed, with 2 columns to the page for easier reading. A section on vitamin deficiencies has been added. The chapter on neoplasia has been almost entirely rewritten to incorporate the results of recent research. The chapter on the principles of infectious diseases has been enlarged. The bibliography has kept pace with the changes in the text and constitutes, as in previous editions, a most valuable feature of the book. These are but a few of the numerous changes and additions that have brought this book up-to-date. About half the text has been entirely rewritten and much of the remaining material has been rearranged. Well over a 100 new illustrations have been provided and photographs and photomicrographs largely replace the older drawings.

The Reviewer finds the book easier to read than previous editions and strongly recommends it, not only as a sound reference, but as an interesting and readable text. It is, in his opinion, the best one-volume textbook of pathology available.

D. C.

Pharmacopœia of the United States of America. Twelfth Revision. By authority of the U. S. Pharmacopœial Convention meeting at Washington, D. C., 1940. Prepared by the Committee of Revision and Published by the Board of Trustees. Pp. 880. Easton, Pa.: Mack Printing Company, 1942. Price, $7.50.

Comparative Vertebrate Anatomy. By LIBBIE HENRIETTA HYMAN, Research Associate, American Museum of Natural History, New York City. Second Edition. Pp. 544; 136 figures. Chicago: Univ. of Chicago Press, 1942. Price, $3.50.

This is a revision of the Laboratory Manual for Comparative Vertebrate Anatomy so popular for 20 years. In this edition the textual material has been elaborated so that the book can serve as a text as well as a laboratory manual. Some illustrations are new, and all are taken from the specimen. W. A.

Fractures and Dislocations. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Surgery (Rush) of the University of Illinois; Attending Surgeon, Presbyterian Hospital; Formerly Attending Surgeon, Cook County Hospital, Chicago, Ill. Fourth Edition. Pp. 1106; 1140 engravings. Philadelphia: Lea & Febiger, 1942. Price, $12.50.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
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PROGRESSIVE THERAPEUTICS AS AIDED BY U. S. PHARMACOPEIA XII

As was pointed out in the May issue of this Journal, the laborious task of the Twelfth Revision of the United States Pharmacopeia has recently been completed. The object of this revision was to bring into the Pharmacopeia the progress relating to therapeutic agents that had been made in the course of the past few years. There can be little doubt that most physicians regard the Pharmacopeia as an important text, since it provides the legal standards for the quality and purity of medicinal agents. More and more physicians have come to prescribe drugs with the term "U.S.P." written after the name, or to use the official title for a drug which insures that a preparation of Pharmacopeial quality will be dispensed. To the extent to which that is done, the Pharmacopeia comes directly into the practice of efficient therapy. Beyond that, however, physicians make very little use of the Pharmacopeia, since they justly think that the details of matters concerning standards and purity are more directly in the domain of the pharmacist and manufacturer than in that of the practising physician. They seldom turn to the Pharmacopeia for therapeutic assistance, since the text contains no direct therapeutic discussions.

We wish to call particular attention, however, to one aspect of the work of Pharmacopeial revision which makes this text, from one standpoint, one of the most important sources of therapeutic information available to the physician, namely, the aspect of scope. What is new in the field of therapy? Do these new preparations represent essential advances, or are they merely duplications and non-essential modifications of old remedies? How do matters stand with the preparations that have been in use during the past decade? No greater burden rests upon the physician who seeks to practise the most advanced and rational therapeutics than the one of selection of drugs. The literature which

usually brings these matters to his attention is voluminous, confusing, and often represents some specific bias. The course of therapeutic progress is devious and difficult. The Scope and Therapeutics Committees of the Pharmacopeia deal specifically with these problems. The selection of drugs is based upon intensive discussions and deliberations of a group of experts in the various fields to which these agents are applied, including physicians, pharmacologists, chemists and pharmacists, representing sufficiently wide experience to insure the inclusion of diversified views. The "additions" as well as the "deletions" of the new Pharmacopeia represent their decisions.

It is the object of this second section of the review to point out, by brief accounts of a few of the more important groups of therapeutic agents which have been adopted in the Twelfth Revision, the type of considerations which go into the final selection of the list of Pharmacopeial drugs. If the physician will familiarize himself with the agents described in the new Pharmacopeia, he will have gone a long way toward solving a very trying problem, on the one hand, of insuring the fact that he does not overlook many significant developments in therapeutics, and, on the other hand, of escaping the deluge of so-called new preparations which have contributed almost nothing of intrinsic value to the efficacy of therapeutic practice. No text other than the Pharmacopeia sets that up as one of its major functions. It should be noted that the discussions of the few groups of agents which follow are intended merely to be illustrative. To consider all the agents of the Pharmacopeia in this manner would carry this review beyond its proper limits.

Antacids. The previous Pharmacopeia described standards for the following antacids: Sodium Bicarbonate, Magnesium Carbonate, Magnesia Magma (Milk of Magnesia), Magnesium Oxide (light), Heavy Magnesium Oxide, Precipitated Calcium Carbonate, Prepared Chalk and Tribasic Magnesium Phosphate. These are described in the forthcoming Pharmacopeia, in addition to four new types of preparations: Tribasic Calcium Phosphate, Aluminum Hydroxide Gel, Dried Aluminum Hydroxide Gel and Magnesium Trisilicate.

The available aluminum hydroxide preparations of commerce vary in their aluminum oxide content, and in their power to absorb acid. The U.S.P. standards require that the aqueous suspension in the form of the gel represents approximately 4% Al_2O_3, and that the average dose of 8 cc. (2 teaspoonfuls) consumes between 100 and 200 cc. of 0.1 N hydrochloric acid. The dose of Dried Aluminum Hydroxide Gel is given as 0.6 gm. (10 grains), and this is required to consume at least 150 cc. of 0.1 N hydrochloric acid.

Magnesium Trisilicate is tested for its power to adsorb methylene blue and also for its acid-consuming capacity. The U.S.P. dose of 1 gm. (15 grains) is required to consume approximately 150 cc. of 0.1 N hydrochloric acid. Standards are provided for a Magnesium Trisilicate Tablet. The 0.5 gm. ($7\frac{1}{2}$ grains) size is usually prescribed. In the form of the tablet the acid-consuming power is somewhat less, namely about 100 cc. 0.1 N hydrochloric acid per gram.

With these new compounds in the Pharmacopeia, advanced principles in antacid therapy are recognized, namely, the control of acidity by physical absorption and reduction of acidity of the gastric juice without complete neutralization or alkalization of the gastric contents. These

compounds reduce the hydrogen ion content of the gastric juice but do not possess the power to alkalinize. In addition to removing hydrogen ions, they exert astringent and coating properties. The trisilicate of magnesium especially forms an adherent gelatinous coating with protracted antacid properties of protective and healing value in peptic ulcer.

The Tribasic Calcium Phosphate (dose 1 gm.; 15 grains) serves not only as an antacid but as a useful source of calcium and phosphorus. This is of some importance, in view of the recent evidence that aluminum hydroxide may precipitate the non-absorbable aluminal phosphate and thereby deplete the body of phosphorus stores, leading to phosphorus deficiency.

Sedatives and Hypnotics. The Pharmacopeia now includes four classes of agents in this group: barbiturates, chloral hydrate, bromides and paraldehyde. Among the barbiturates, Barbital, Barbital Sodium, Phenobarbital and Phenobarbital Sodium represent the older preparations. Their duration of action is long. The addition of the Elixir of Phenobarbital meets the need for a liquid barbiturate preparation. It contains 15 mg. ($\frac{1}{4}$ grain) of Phenobarbital to the teaspoonful. It is especially useful in children. Pentobarbital Sodium has been added as a representative of the rapidly acting barbiturates. For sustained action as a sedative during the day, Phenobarbital is most useful. It may also be used in the same or somewhat larger doses at bedtime to promote sleep. Barbital may be used in a similar manner, although it is more commonly employed in the form of a 5 grain tablet at bedtime. With respect to their therapeutic actions, Barbital and Phenobarbital are interchangeable. There is a significant difference in their mode of elimination. The largest part of a dose of Barbital is excreted by the kidney, while in the case of Phenobarbital, only a small part of the dose is excreted in this manner, the rest being destroyed in the body. If it is necessary to secure somewhat stronger action to induce sleep, one often finds that Pentobarbital Sodium is more satisfactory, since a larger dose may be given, 0.1 to 0.2 gm. ($1\frac{1}{2}$ to 3 grains), with less risk of a protracted hangover the following day. The sodium salts of the barbiturates are soluble and somewhat more rapidly absorbed than the parent substances. They are particularly important in relation to the use of barbiturates by parenteral administration. The only one that can be given subcutaneously is Phenobarbital Sodium. Its solution is nearly neutral, while the solutions of the other barbiturates are strongly alkaline and irritant. The introduction of standards and methods for the assay of tablets and capsules of the barbiturates gives further assurance of uniformity among the dosage forms in which these compounds are most commonly employed.

In cases of epilepsy, in which very large doses of bromides are sometimes given, there are occasions when large amounts of sodium base are undesirable, and others in which large amounts of potassium might prove harmful. The Pharmacopeia has therefore included both Sodium Bromide and Potassium Bromide. Calcium Bromide and Ammonium Bromide have been deleted as unnecessary duplications. Carbromal, one of the hypnotics of the urea group, has been dropped. It has a very limited sedative action which can be satisfactorily secured from small doses of Phenobarbital.

It is important to have at one's command more than one sedative or hypnotic agent because of the special problems presented by different patients. Often the patient is hypersensitive to one and not to another. On the other hand, the large number of hypnotic agents available in commerce represents a great deal of duplication which leads only to confusion and inefficient therapy. The simplified list of preparations in the new Pharmacopeia meets all essential needs.

Diuretics. The rôle of diuretics in the medicinal control of cardiovascular disorders has increased greatly in recent years. Knowledge concerning the conditions to which these may be usefully applied, their dosage and methods of administration, has made great strides. The Scope and Therapeutics Committees of the Pharmacopeia have selected from the large number of available preparations a small group of the most effective compounds. A diversity of therapeutic indications are taken into account.

Among the xanthines there are Theophylline, dose 0.2 gm. (3 grains); Theophylline Ethylenediamine, dose 0.2 gm. (3 grains); and Theobromine and Sodium Acetate, dose 0.5 gm. (7½ grains). Standards for the most frequently used dosage forms are described: Theobromine and Sodium Acetate Capsules, Theophylline Tablets, Theophylline and Sodium Acetate Tablets, and Theophylline Ethylenediamine Tablets. While they all possess the same type of diuretic action, there is taken into account the belief that some patients tolerate one of the xanthines better than another. The doses stated are not strictly comparable in terms of the purine base, but are sufficient as a starting point in therapy.

Some patients are so sensitive to the central stimulant action, or to the local irritant action of the entire group of xanthine diuretics that wakefulness, nervousness, or digestive upsets occur before sufficient is taken to affect the edema. In such cases Urea or Ammonium Chloride may be substituted. The Urea is given in such large doses, often as high as 1 ounce 3 times a day, that it is best prescribed in a powder with directions to dissolve the dose in chilled sweetened orange juice. The Pharmacopeia describes standards for Ammonium Chloride Capsules of 1 gm. (15 grains) each, and 1 or 2 capsules are usually taken every 4 hours, although much larger doses are sometimes needed. It is frequently prescribed in enteric coated tablets to overcome the irritant action in the stomach, although there is a good deal of doubt as to whether that result is accomplished by the enteric coating.

The organic mercurials are included for those cases in which oral diuretics do not suffice. The new Pharmacopeia describes these in the form of ampoule solutions: Mercurophylline Injection (Mercupurin) and Mersalyl and Theophylline Injection (Salyrgan with Theophylline). As indicated by the Pharmacopeial directions, experience seems to favor the intramuscular route, and the 1 cc. dose of the former and the 2 cc. dose of the latter, although both doses are used for both preparations, and the intravenous route is frequently preferred. It is noteworthy that, while the previous Pharmacopeia described the mercurial alone, the present one directs the use of the combination with a xanthine. The new text has taken account of the more recent evidence indicating that the addition of a xanthine to an organic mercurial reduces the local irritant action and toxicity. It is important to have more than one

organic mercurial available because there are patients hypersensitive to one who show no intolerance to another.

For the groups of edematous patients, especially those with chronic nephritis, in whom all the foregoing are sometimes ineffectual, Potassium Nitrate or Potassium Chloride are sometimes of great benefit. The potassium salts lead to the accumulation of potassium base and excretion of sodium which in turn results in a diuresis. Standards are provided for the Potassium Chloride Tablets which may be prescribed in doses of 1 or 2 gm. (15 to 30 grains) 3 times a day.

Antiluetic Agents. While there has been a great deal of active research in the field of antiluetic therapy during the past 10 years, it is noteworthy that no extensive revision in the scope of essential agents has become necessary in the new Pharmacopeia. Scores of arsenic and bismuth compounds and their preparations are marketed, but there is indeed a question whether most of them have brought about any significant improvement in the treatment of syphilis. Such preparations as Bismarsen representing combined arsenic and bismuth therapy in one compound for intramuscular use, and Sobisminol Mass for oral treatment of syphilis have excited a great deal of interest, but they cannot be considered as having established superiority for routine therapy. Mapharsen, the hydrochloride of arsenoxide, although a relatively new compound, has received extensive trial and reports of favorable experience are so abundant that little doubt remains concerning the fact that it will come to play an important rôle in the treatment of syphilis. The largest experience in effective antiluetic therapy, however, relates to the limited group of agents official in the forthcoming Pharmacopeia.

Among the arsenicals, the standards for Arsphenamine and Neoarsphenamine are carried over into the new Pharmacopeia. Tryparasamide, dose 2 gm., is described for the special problems of neurosyphilis. While there is no question of the superiority of intravenous arsenical treatment, there are occasions when the intravenous route is not feasible, especially in children. This need has been met by the inclusion of Sulfarsphenamine, dose 0.45 gm. (7 grains), in the new Pharmacopeia. It is recognized to possess greater toxicity for adults than for children, but there are indications of improvement in the method of manufacture which has reduced its toxicity.

For oral treatment, Sodium Iodide and Potassium Iodide are continued.

There are several mercury compounds. Mercuric Salicylate is an insoluble preparation employed in the form of a suspension in oil. The standards for such an oily suspension are now described under Mercuric Salicylate Injection. The drug is usually administered in a dose of 1 cc. of the suspension by intramuscular injection containing approximately 0.1 gm. (1½ grains) of Mercuric Salicylate and representing approximately 50 mg. of mercury. Mercuric Succinimide is an organic mercurial compound containing slightly less mercury and represents a very soluble mercury preparation. It is relatively nonirritant by comparison with inorganic soluble mercurials such as bichloride of mercury. It is administered intramuscularly in aqueous solutions in doses of 15 mg. (¼ grain). It is usually available in 2.5% solutions, dose 0.6 cc. The difference in the dosage from that of

Mercuric Salicylate should be noted. The average intramuscular dose of the insoluble salicylate represents about 50 mg. of mercury, while that of the soluble succinimide represents only about 7.5 mg. of mercury. A noteworthy change in the new Pharmacopeia is the reduction in the number of mercury compounds for the treatment of syphilis which represented unnecessary duplication. The Yellow Mercurous Iodide has been deleted. Also, in line with the diminishing use of oral antiluetic mercurial therapy, oral doses are no longer provided in the Pharmacopeia for Mercury Bichloride and Mercuric Succinimide. The only mercurial preparation for oral administration of mercury as an antiluetic agent contained in the present Pharmacopeia is the Mercury with Chalk prescribed in an average dose of 0.25 gm. or 4 grains, representing 95 mg. of mercury.

Among the bismuth preparations there are included Bismuth and Potassium Tartrate, and the Bismuth Subsalicylate. The Bismuth and Potassium Tartrate is a compound very soluble in water and rapidly absorbed. It is administered by intramuscular injection in an average dose of 0.1 gm. ($1\frac{1}{2}$ grains), representing about 62 mg. of bismuth. This compound must be stored in light-resistant containers because it darkens on exposure to light. The Pharmacopeia provides standards for the two common dosage forms in which this material is administered, namely, in the form of an aqueous solution in which the absorption is most rapid, and an oil suspension in which the absorption is delayed. The usual aqueous preparations contain 50 mg. of the compound in 2 cc., and the oil suspensions 100 mg. in 2 cc. The oil suspension of Bismuth and Potassium Tartrate is often given in twice the dose of that in the form of the aqueous solution and the intervals between injections are usually 7 days in the case of the oil suspension as against 2 to 3 days in the case of the more rapidly absorbed aqueous solution.

Bismuth Subsalicylate is an insoluble compound. The new Pharmacopeia provides the standards for the Bismuth Subsalicylate Injection, the oily suspension in which it is usually employed. The average dose is 0.1 gm. ($1\frac{1}{2}$ grains) by intramuscular injection, representing about 57 mg. of bismuth, and is commonly available in the oily suspension containing this dose in 1 cc. Bismuth Subsalicylate appears to be the most widely approved bismuth preparation for the treatment of syphilis.

Vitamins. The forward strides in vitamin research in recent years and the avalanche of vitamin preparations of commerce have created a state of confusion bordering on chaos in therapeutics. Some of the earlier discoveries of vitamins were made in relation to a search for the cause of well-known diseases such as pellagra, beriberi and scurvy. When the purified materials were isolated, physicians were in possession of considerable knowledge of the uses to which they could be put. It is otherwise in the case of several of the vitamin compounds more recently brought to light. The search for the latter was correlated more directly with the growth and metabolic abnormalities in experimental animals. For example, pantothenic acid was developed in relation to the cure of the nutritional dermatitis of chicks, pyridoxine in relation to the cure of the pink or florid dermatitis (acrodynia) in rats kept on a deficient diet, vitamin E (wheat germ oil or alpha-tocopherol) in relation to the prevention or cure of neuromuscular degeneration and reproductive

disorders due to dietary deficiencies in lower animals. Little is known, however, of the rôle of these and other of the newer vitamins such as biotin and choline in human disorders, although numerous suggestive observations in man have been made. An authoritative expression on the scope of the therapeutically effective vitamins by the Pharmacopeia is therefore very welcome.

The widely different compositions and potencies of market preparations present another trying problem for the practitioner. There is the further fact that he should be assured not only that the labeled potency is correct, but that the method by which potency is determined gives results which are applicable to humans. There are several methods of assay for most of the vitamins, and they do not always give the same results when two materials are compared. There is evidence, for example, that, in relation to vitamin D, the liver oil of the blue-fin tuna is about 6 times as effective in the rat as in the chick, while the oil of the white sea-bass is only about one-half as effective in the rat as in the chick. This is probably due to the different composition of specific sterols in the two oils, one of which is more effective in one species than in the other. The selection of a proper bioassay method which will establish constant potency of vitamin materials for man is, therefore, a matter of major importance.

The previous Pharmacopeia described only two materials for their vitamin content, vitamins A and D, in the form of Cod Liver Oil (dose 8 cc. daily or at least 600 units of vitamin D and 6000 units of vitamin A), and the Emulsion of Cod Liver Oil (dose twice as large). These doses provide adequate intake of the two vitamins for prophylactic purposes. At this point it may be stated that all the Pharmacopeial doses of vitamins apply to prophylaxis. Larger amounts are usually necessary in established deficiency diseases. The subject of the vitamins was given intensive study by several subcommittees of the U. S. Pharmacopeial Revision Committee, the committees on Scope, Therapeutics, Bioassay, and the U.S.P. Vitamin Advisory Board. The essential progress of the past 10 years has now been incorporated in the new text. There are described suitable preparations of all the vitamins of established value, proper dosage forms, methods of assay, and average dosage.

For the treatment of vitamin A deficiencies (nictalopia, xerophthalmia, follicular keratosis), the Pharmacopeia provides a rich source of vitamin A in the preparation, Oleovitamin A. This preparation represents a concentrated solution in oil of natural vitamin A obtained from fish liver sources. It is required to contain at least 50,000 units of vitamin A per gram (above 50 drops) and not more than 1000 units of vitamin D. It is more suitable as a clinical source of vitamin A than Cod Liver Oil. The prophylactic daily dose of this preparation is 0.1 cc. ($1\frac{1}{2}$ minims or 5 drops), representing at least 5000 units of vitamin A with a negligible amount of vitamin D (100 units or less). To obtain the same amount of vitamin A it would be necessary to give 2 teaspoonfuls of Cod Liver Oil which has, from certain standpoints, the further disadvantage of the presence of large amounts of vitamin D. The Pharmacopeia also describes Oleovitamin A capsules, one containing 5000 units and the other 25,000 units. One of these smaller capsules daily is used for prophylaxis, and the latter for massive dosage in

treatment. It is noteworthy that for vitamin A therapy the Pharmacopeia does not provide any carotene preparations or synthetic materials of vitamin A. The use of vitamin A parenterally also seems to be too unsettled for routine application.

As a concentrated source of vitamin D for the prevention and treatment of rickets and other vitamin D deficiencies, the new Pharmacopeia describes the preparation Synthetic Oleovitamin D (viosterol in oil, activated ergosterol in oil). It is provided only in solution because dry pure viosterol loses potency fairly rapidly. The text requires that the label shall indicate whether the preparation contains vitamin D_2 or vitamin D_3, because there is some doubt as to the identity of their actions in man. In this connection it should be noted that there are several antirachitic sterols from vegetable and animal sources. The two most important ones are ergosterol (from vegetable sources) and 7-dehydrocholesterol (from animal sources). These compounds are isomers and acquire antirachitic functions through the action of specific radiant energy (ultraviolet rays) which leads to a shift of the position of the double bond in the molecule. This process is referred to as activation. Activated ergosterol is a crystalline compound also called vitamin D_2, and activated 7-dehydrocholesterol is also called vitamin D_3. These two vitamin D sterols have different relative potencies in different species of animals. In the chick, the rat unit of the vitamin D derived from cholesterol (D_3) is nearly 20 times as effective as the rat unit of vitamin D derived from ergosterol (D_2). The vitamin D from the two sources is therefore not identical, although the evidence indicates that their behavior in man parallels fairly closely their behavior in the rat. The rat method, therefore, has been adopted by the Pharmacopeia for the standardization of vitamin D materials.

The preparation Synthetic Oleovitamin D has the advantage over Cod Liver Oil for the prophylaxis and treatment of rickets that it is highly concentrated, it is odorless, and has a bland taste. It contains not less than 10,000 U.S.P. units of vitamin D per gram. Since the prophylactic requirement is only about 1000 units daily, at least this amount will be present in a dose of the oil of 0.1 cc. or $1\frac{1}{2}$ minims or 5 drops. It has the further advantage over Cod Liver Oil that large doses of vitamin D can be administered without simultaneous use of the large amounts of vitamin A present in Cod Liver Oil.

For the problems of mixed fat-soluble vitamin deficiencies in which it is desirable to use both vitamins A and D, the Pharmacopeia provides 4 new preparations, namely, Cod Liver Oil, Emulsion of Cod Liver Oil, and 2 new preparations, Oleovitamin A and D, and Concentrated Oleovitamin A and D. The Oleovitamin A and D is intended as a substitute for Cod Liver Oil. It is of particular importance in relation to the shortage of natural Cod Liver Oil at the present time. The vitamin A in this preparation comes from natural fish liver sources, and the vitamin D content may be either from synthetic or natural sources. The dosage is the same as for Cod Liver Oil, 8 cc. or 2 teaspoonfuls representing approximately 700 units of vitamin D and 7000 units of vitamin A. The potency of this preparation is likely to be more uniform than that of Cod Liver Oil because, while the Pharmacopeia fixes its potency, the text specifies only a minimum potency for Cod Liver Oil. There remains to be considered, however, the possibility that

there may be factors of therapeutic value in Cod Liver Oil which are not disclosed by the specific tests for vitamins A and D.

The preparation Concentrated Oleovitamin A and D provides a highly concentrated source of both vitamins A and D. It represents for the most part a combination of the preparations Oleovitamin A and Synthetic Oleovitamin D. The standards require a fixed content of both vitamins A and D. The daily prophylactic dose of this preparation is 0.1 cc. ($1\frac{1}{2}$ minims or 5 drops), representing approximately 5000 units of vitamin A and 1000 units of vitamin D. This is an extremely useful preparation for both the prophylaxis and the treatment of conditions requiring the combination of the two vitamins. A dose of 5 drops of this preparation provides approximately the same amount of vitamins A and D as is found in a 2 teaspoonful dose of a good grade of Cod Liver Oil. This dose is contained in the Pharmacopeial Capsule of Oleovitamin A and D. The capsule is a convenient dosage form, 1 capsule daily being required for prophylactic purposes.

For the treatment of alcoholic polyneuritis, the beriberi heart and the wide variety of conditions associated with vitamin B_1 deficiency, the Pharmacopeia provides the preparation Thiamine Hydrochloride with an average daily dose of 5 mg. ($\frac{1}{12}$ grain). The chemical method of assay is described for this compound. There is also included the tablets of Thiamine Hydrochloride which are generally provided in sizes of 3, 5 and 10 mg. The potency of these tablets is assured by a detailed colorimetric test described in the Pharmacopeia. The text also describes a biologic test, the rat method, involving the cure of polyneuritis in rats, for assaying the thiamine content of preparations containing this vitamin. It should be noted that the elixir of thiamine hydrochloride, which is fairly popular, is not included because of the instability of such liquid preparations. The Pharmacopeia also includes Rice Polishings (Tikitiki) as a rich crude source of the antineuritic vitamin.

Nicotinic Acid is the most important single member of the B complex responsible for the curative effects of such food products as liver, wheat germ and yeast in the multiple deficiency disease known as pellagra. The synonym Niacin has been adopted in order to avoid the confusion with nicotine, the toxic alkaloid of tobacco. The average dose of Niacin, as given by the Pharmacopeia, is 25 mg. ($\frac{3}{8}$ grain). Much larger doses are often used. Standards are also provided for Nicotinic Acid Tablets, of which the common sizes are 25, 50 and 100 mg. Nicotinic Acid often produces a histamine-like flush which is sometimes quite disturbing. This effect is much less pronounced in the amide of Nicotinic Acid. The Pharmacopeia has therefore also included Nicotinamide (Niacinamide), and the tablets of this compound in dosages similar to Nicotinic Acid. The amide is about 60 times as soluble in water as the Nicotinic Acid. Both forms are desirable at the present time, because it is not satisfactorily established that the two are in all respects interchangeable in therapy. Chemical standards are provided for these pure compounds, as well as for their tablets. In addition, there is included a biologic method of assay for Nicotinic Acid in mixtures in which it may be contained. This method is based on the effect of Nicotinic Acid on the liberation of acid by the *Lactobacillus arabinosis*.

The therapeutic usefulness of other members of the vitamin B group does not appear to be sufficiently established to have warranted their inclusion in the new Pharmacopeia at the time of the preparation of the original text, namely, Pantothenic Acid, Pyridoxine and Choline. There are no well-established human deficiencies which can be ascribed with certainty to the lack of these materials. Nevertheless, they are found in human tissues and undoubtedly play a rôle there. The special conditions arising during the war which may involve gross dietary defects among armed as well as civilian groups make it desirable to have available a concentrated mixture of the members of the B complex in such proportions as seem appropriate from the limited experience that exists. The Supplement to the Pharmacopeia is therefore to describe the standards for Calcium Pentothenate and Pyridoxine Hydrochloride. There is to be a tablet and a capsule, each containing the mixed vitamins of 250 mg. of Liver Extract fortified with the following: 1 mg. of Thiamine Hydrochloride, $1\frac{1}{2}$ mg. Riboflavin, 10 mg. Nicotinamide, 5 mg. Calcium Pantothenate and 1 mg. Pyridoxine Hydrochloride. There is also to be a preparation of a powder of Liver Extract rich in vitamins for oral administration and a similar material in liquid form for parenteral administration. In addition there is to be a solution of Liver Extract rich in B vitamins for parenteral administration, also fortified by the addition of small amounts of the following: Choline, Nicotinic Acid, Pantothenic Acid, Pyridoxine Hydrochloride and Riboflavin.

For the prophylaxis and treatment of scurvy and other vitamin C deficiencies, the Pharmacopeia includes Ascorbic Acid and the Tablets of Ascorbic Acid which are commonly available in doses of 25, 50 and 100 mg. The average daily dose which extensive experience has established is 50 mg. ($\frac{3}{4}$ grain) by oral administration. Chemical and colorimetric methods are described for the standardization and assay of the crystalline compound as well as the tablets.

Antimalarials. The use of cinchona alkaloids in the treatment of malaria presents a special problem at the present time. Prior to the war, about 90% of the world's cinchona bark came from Java. This bark was obtained chiefly from high quinine-yielding trees and represented the chief source of the world's supply of quinine. The Pharmacopeia has included Quinine, Quinidine and their salts for use chiefly in the treatment of malaria, although relatively small amounts are used also in the treatment of disorders of cardiac rhythm. These sources of Quinine have now been shut off by the war in the Pacific, with the result that attention has again been focused on the use of the other alkaloids of the cinchona tree as antimalarial agents. There are now numerous studies indicating that the mixed alkaloids of cinchona bark, even those mixtures relatively poor in quinine, are nearly, if not quite, as effective as Quinine itself in the control of malaria. These mixtures of the alkaloids of cinchona bark are called Totaquine. In view of the fact that the mixtures of cinchona alkaloids from different sources and different barks show wide differences in composition, the new Pharmacopeia has adopted a set of standards for Totaquine which is for the most part now secured from sources in Central and South America. The sources now available have a rather low content of Quinine, and while the U.S.P. XII preparation was at first required to contain not

less than 10% of anhydrous quinine, the difficulty of maintaining this standard in cinchona bark from present sources has led to the proposal to lower the minimum requirements of quinine in Totaquine to 7%. Totaquine as a substitute for quinine is administered in somewhat larger doses than quinine, namely, 0.6 gm. (10 grains), 3 times daily. It is highly probable that little is lost in the efficiency of the treatment of malaria by the substitution of Totaquine. In addition, it provides an antimalarial agent which is less costly than quinine.

Among the synthetic antimalarial substitutes for quinine, the Pharmacopeia has included Quinacrine Hydrochloride and its tablets. This is a bright yellow powder, soluble in water and possessing a bitter taste. Like quinine, it is effective chiefly against the asexual forms of the Plasmodium. The Pharmacopeial dose is 0.1 gm. ($1\frac{1}{2}$ grains), which may be given in the form of the tablet 3 times daily for a period of about 5 days in the average case of malaria. This material is an acridine dye and causes a somewhat persistent yellow staining of the tissues of the patient. Unlike quinine, its excretion is fairly slow and often as long as a month or two is allowed to elapse before a course is repeated. The toxicity of this compound by oral administration is relatively low and it is not apt to cause cinchonism. While there is little doubt about the value of Quinacrine in the average case of malaria, there is still some question regarding the relative efficacy of the two compounds and the specific circumstances under which Quinacrine is preferable to Quinine. The introduction of Quinacrine into the Pharmacopeia, however, is of special importance at the present time, in view of the serious shortage in the available supply of natural antimalarial agents.

Amebicides. For the treatment of amebiasis, 3 preparations are described, Chiniofon, Emetine Hydrochloride and Carbarsone. While all 3 compounds are effective in the cure of amebiasis, they do not represent duplications, because each possesses a special field of usefulness in the treatment of this disease. Amebiasis is essentially an infection of the large intestine with systemic invasion. The parasites are present in the feces, in the wall of the intestine, and within the tissues of the host such as the liver. Chiniofon, one of the iodohydroxyquinoline compounds, is a pale yellow, bitter powder, fairly soluble in water. It has a fairly high amebicidal activity. The Pharmacopeial dose is 1 gm. (15 grains), which may be given 3 times daily by oral administration. It is available in Pharmacopeial Tablets of Chiniofon, 0.25 gm. (4 grains) each. A similar dose may be given as a retention enema in which 1 gm. is dissolved in 200 cc. of water. These doses are repeated daily, usually for a course of about 10 days, and in some cases oral and rectal administration may be combined. The toxicity of this compound is relatively low, since little of it is absorbed, although occasionally enough is absorbed to produce injury of the liver. It is, however, irritant to the gastro-intestinal tract and occasionally causes diarrhea. In view of the limited absorption, this compound is relied upon chiefly for the eradication of the parasites within the lumen of the intestine. Since in most cases of amebiasis the parasites are also present within the tissues, Chiniofon alone is responsible for a very low proportion of complete cures.

In contrast to Chiniofon, Emetine Hydrochloride is used chiefly

for the eradication of the protozoa present within the tissues of the host. This represents for the most part a parenteral form of treatment of amebiasis. The use of ipecac, from which Emetine is obtained, or Emetine itself by oral administration, is unsatisfactory because even subeffective doses are highly emetic. Emetine Hydrochloride is a slightly yellowish soluble powder which is influenced by light and is therefore preserved in light-resistant containers. It belongs to the group of alkaloids. The Pharmacopeia provides the standards for the ampoule solution under the name of Emetine Hydrochloride Injection. The usually available ampoules contain from 20 mg. ($\frac{1}{3}$ grain) to 60 mg. (1 grain) in 1 cc. The injection is given deep into the muscle because of the irritation produced by subcutaneous injection which results in painful nodules. Emetine Hydrochloride is the safest of the amebicidal agents in the treatment of amebic hepatitis and abscess of the liver, but when used alone it also will eradicate the disease in only a small proportion of cases, about 1 in 6, because it has little effect upon the amebæ present in the lumen of the intestine. It is therefore of little value in carriers. It should be noted at this point that in a fairly large proportion of cases, amebiasis produces no symptoms, and in only a relatively small proportion does it give rise to diarrhea. The toxicity of Emetine Hydrochloride is high, bordering closely on the therapeutic doses, and in a large proportion of cases overlapping the therapeutic doses. Bloody diarrhea, cardiac changes and collapse are the outstanding effects. The use of Emetine is most suited for the treatment of amebiasis in the patient confined to bed. The average Pharmacopeial dose is 60 mg. (1 grain) intramuscularly, which may be repeated daily in a course lasting about 10 days. When given in this way, absorption is in evidence fairly promptly (about 30 minutes), but elimination is quite slow, so that traces may still be found in the urine several weeks after the dose. For this reason it is unwise to repeat a course of treatment for at least 2 weeks. It is usually necessary to supplement this treatment with one of the compounds which is more effective upon the organisms present in the lumen of the intestine, such as Chiniofon or Carbarsone.

Carbarsone is a new addition to the Pharmacopeia. It is a pentavalent organic arsenical containing about 28% of arsenic. It is a white powder, almost tasteless, and insoluble in water. It provides a means for the oral treatment of amebiasis and attacks the organisms in all their locations, in the lumen of the intestine as well as in the tissues. It is therefore useful in carriers. It is absorbed through the gastro-intestinal tract and slowly excreted. A course of treatment with this compound is also limited to about 10 days, with intervals of about 2 weeks between courses. The Pharmacopeial dose is 0.2 gm. (3 grains), which may be taken in capsules 3 times daily. The free forms of the protozoa present in the lumen of the intestine are often more effectively eradicated by the rectal administration of the carbarsone in the form of an enema, 2 gm. (30 grains) dissolved in 200 cc. of 2% sodium bicarbonate (the compound is soluble in alkalis) given every other day. This is essentially an ambulant form of treatment. The dangers from Carbarsone are the dangers of other arsenicals, namely, exfoliative dermatitis and hepatitis. As already stated, in cases of

liver disease from whatever cause, Emetine is preferable for the control of amebiasis.

There are still other agents about which useful comment could be made for the aid of the practitioner. These include, for example, some of the approved sex hormones, synthetic vitamin K or menadione, etc. However, space is lacking for detailed comment on these substances. It is hoped that this review, together with the one published in May, may serve to rouse the practitioner's interest in becoming better acquainted with the great value to him which lies between the covers of U.S.P. XII.

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RADIOLOGY

UNDER THE CHARGE OF
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THE PANCREAS—THE SMALL INTESTINE

The Pancreas. The Roentgen study of disease of the pancreas is difficult because the organ cannot be visualized directly and because it is one of the few structures contained within the abdomen which has not yet been made demonstrable through the retention of some radiopaque substance. Because of this, Rendich, Poppel and Cove[8] stated that it was necessary to resort to indirect methods. These indirect methods had their chief value in the detection of alterations in the contour of contiguous structures, notably the barium-filled duodenum or the distended stomach, resulting from pathologic changes which modified the volume or the form of the pancreas.

They credited Dickson[3] with calling attention, in 1923, to pressure deformities of the barium-filled stomach and duodenum produced by carcinoma of the pancreas. Butler and Ritvo,[2] they stated, reported in 1931 that they had found displacement with widening of the duodenal curve to be significant of pressure from a tumor of the head of the pancreas. Rigler[9] was quoted as having confirmed the opinion of Butler and Ritvo[2] in 1933 and to have added the note that in his experience the stomach was often displaced upward and forward in the presence of carcinoma of the body and the tail of the pancreas, while the transverse colon was displaced downward.

Engel and Lysholm,[4] they found, had described a method for roentgenologic observation of the pancreas in 1934. The stomach was inflated with carbon dioxide and, following this inflation, roentgenograms were made with the patient in the lateral, prone and antero-posterior positions. Enlargement of the pancreas was indicated by an increase in the space which it normally occupied and was made evident by protrusion into the gas-filled stomach from behind. These authors were interested in the findings of Hunt, Hicken and Best[6] in exploration

of the biliary ducts with the aid of cholangiography during and after operation, published in 1937. The contrast substance was injected, usually through a tube. In the presence of carcinoma of the head of the pancreas, there was no filling of the lower segment of the common duct. The duct was cut off abruptly in the cholangiogram and often in a transverse direction rather than in a tapering or funnel-shaped pattern. The patent proximal portion of the common duct and the cystic duct were unusually widened. A reflux of radiopaque material into the pancreatic duct was observed in 5 of their cases, the duct being filled for a distance of 2 to 9 cm. Such reflux, they considered, depended on the anatomic relation of the common duct, the pancreatic duct, the ampulla of Vater, and the duodenum. It also depended on the terminal sphincteric mechanism. Giordano and Mann[5] were quoted as having found that reflux was impossible in about one-third of all subjects because the pancreatic and common ducts opened separately into the duodenum.

Rendich, Poppel and Cove[8] called attention to the dependence of roentgenologic criteria on gross pressure changes. While these gross pressure changes might result from any enlargement of the head of the pancreas, from regional retroperitoneal lymph node enlargement or from the occurrence of any retroperitoneal mass in the pancreatic area, they were of the opinion that experience in the correlation of roentgenologic evidence with characteristic clinical and laboratory findings in a series of cases warranted them in often parenthetically suggesting the more likely specific etiology. Briefly outlining the anatomic relations of the pancreas to contiguous viscera and organs, they stated the signs which, in their opinion, indicated the presence of a mass in the region of the pancreas. Enlargement of the duodenal loop or widening of semicircular arc described by the duodenum might vary according to the habitus of the individual. It could be only an apparent enlargement in the presence of the hypersthenic habitus, in which the stomach is highly placed and almost horizontal in position; the duodenal loop in such individuals when fully exposed appears to be enlarged. Enlargement alone is consequently less significant in the hypersthenic person but very significant in the sthenic or hyposthenic subject. They considered it mandatory in the examination of the hypersthenic type of individuals, who as a group seemed to them to be much more frequently the subjects of biliary tract or pancreatic pathology, to demonstrate, in addition to the enlargement, some evidence of extrinsic pressure on the inner concave border of the descending duodenum. Extrinsic pressure, in their experience, by its ironing-out effect, changed the direction of the medial ends of the horizontal duodenal mucosal folds (*valvulæ conniventes*) so that they became internally concentric with the duodenal lumen and were visualized in the roentgenogram as a border limiting the medial wall of the barium-filled descending duodenum. The density of the mucosal folds was directly proportional to the degree of extrinsic pressure from the space-occupying mass in the region of the head of the pancreas. They found this sign to be an early one, discernible prior to the occurrence of any enlargement or displacement. In the presence of severe pressure, the pattern of the valvulæ conniventes might be greatly altered or even completely obliterated.

Displacement of the duodenal loop toward the right and anteriorly

by space-occupying masses in the region of the head of the pancreas they found to be one of the later signs. The displacement, in their experience, might be general and uniform or it might be simply a localized indentation on the inner concave border of the duodenal loop. They found the stomach to be displaced upward and forward in the presence of a large mass. Enlargements in the region of the body and tail of the pancreas did not affect the duodenal loop but produced downward and anterior displacement of the transverse colon and proximal jejunum and occasional upward and forward displacement of the stomach.

Fixation of the duodenal loop was noted by them, especially of the medial wall. This, they thought, might impair the normal expansion which was usually observed at the time of the passage of increased amounts of opaque medium. Diminished caliber of the lumen of the duodenum was a feature in some cases, sometimes severe enough to result in duodenal obstruction. Alterations in peristalsis were found to be significant; these might be seen as diminishing or even absence of the peristaltic waves. Antiperistalsis might even occur in some cases.

Other characteristic findings were the presence of a palpable mass, the downward and forward displacement of the mid-transverse colon and a filling defect on the outer wall of the descending duodenum with displacement of the duodenum medially. This latter finding, due to an enlargement of the gall bladder, in the presence of painless jaundice of increasing severity, they considered suggestive at least of carcinoma of the common duct or of the ampulla of Vater.

The most common morbid processes occurring in the region of the head of the pancreas that were capable of producing identical roentgenologic signs were, in their experience, malignant new growths involving the head of the pancreas, enlargement of retroperitoneal lymph nodes from (*a*) primary malignancies, (*b*) metastatic malignancies or (*c*) inflammatory lesions, such as infectious mononucleosis, pancreatitis, retroperitoneal tumors, cysts of the head of the pancreas, aneurysm of the anterior wall of the abdominal aorta, amyloidosis of the pancreas and upward traction of the duodenum in some cases of diaphragmatic herniation of the stomach. Pancreatitis might vary from simple edema secondary to involvement of the biliary tract by pathologic processes to chronic pancreatitis with or without biliary calculi.

The pancreas might be the seat of diffuse parenchymal calcification, calculi of varying size and shape might be found in the duct system or a combination of both might be found. The relative frequency of occurrence of each of the individual types was indicated by the fact that Beling, Baker and Marquis[1] were only able to find previous reports of 13 cases of disseminated calcification in their review of the literature on this subject. Calculi, they found, occurred more frequently in the head, less frequently in the body, and comparatively rarely in the tail of the pancreas. Symptoms, all indicative of more or less obstruction in the main ducts, varied widely and might even not present in the earlier stages of the disease. The average age of patients in whom pancreatic calcification occurred was 40 years, but because cases had been reported in which the onset occurred as early as 6 years of age, roentgenograms made of the abdomen of children should be carefully inspected in all doubtful cases. The condition, in their experience,

occurred predominantly in males. Calcification probably occurred secondary to repeated attacks of pancreatitis. Symptoms were usually referable to the gastro-intestinal tract and were severe enough to suggest Roentgen investigation. In a study of the roentgenograms made in 754 consecutive examinations of the gastro-intestinal tract, they found but 1 case showing disseminated calcification and 7 others that suggested calculi in the pancreatic duct system. In the majority of the roentgenograms made in such examinations, the shadow of the opaque media in the stomach or in the colon might obscure the pancreatic area, or flakes of barium in the small intestines might make recognition and differentiation of pancreatic calculi difficult if not impossible. They found it expedient to have a plain roentgenogram made prior to the administration of any type of opaque medium; this should encompass not only the critical area but also the corresponding area to the left of the spinal column. When suggestive shadows were found to be present, further roentgenograms made with the patient in the lateral position were ordered. The indirect methods heretofor described were found helpful. Roentgenograms made in stereoscopic sets were helpful only in those cases where calcifications were found present and they were not considered essential unless other tests were inconclusive. These other tests included blood amylase and lipase determinations and analysis of the pancreatic secretions recovered through an indwelling duodenal tube, both with and without the use of secretin.

The Small Intestine. The incidence of lesions of all types, blastomatous and non-blastomatous, is very low in the small intestine, and the roentgenologic examination of the small intestine, compared to that of the divisions of the alimentary tract above and below it, is an arduous and time-consuming procedure. To many examiners it seemed possible to learn comparatively little about the roentgenologic manifestations of the lesions affecting the lower part of the duodenum, the jejunum and the ileum. Weber and Kirklin[11] noted a renewed interest in the application of roentgenologic methods to the diagnosis of lesions of the small intestine in the last decade.

There were certain clinical syndromes in the presence of which the diagnosis of "gastro-intestinal lesion" was imperative, even when all preoperative objective diagnostic tests failed to exhibit the pathologic process responsible for them. Proved gastro-intestinal bleeding was an outstanding example of such an imperative clinical situation. After the esophagus, stomach, duodenum and colon were eliminated as possible sites of the hemorrhagic lesion by the judicious use of roentgenologic and endoscopic tests, it was certainly justifiable to conclude that if a gastro-intestinal lesion existed at all, the small intestine was harboring it. Under most circumstances sufficient grounds for the institution of diagnostic laparotomy might thus be established.

It was better, of course, first to exhaust all other means of localizing the lesion, but these authors felt that a special roentgenologic examination of the small intestine could be made to yield very satisfactory diagnostic results frequently enough, at least, to warrant its application whenever the condition of the patient permitted it.

In a tabulation of 108 cases of malignant lesions of the small intestine, C. W. Mayo[7] showed the jejunum to be the segment of the small intestine most frequently affected by malignant tumors, while the other

segments, the duodenum and ileum, were involved one about as frequently as the other. In an analysis of the benign lesions of the small intestine seen in the Mayo Clinic from 1907 to 1939, inclusive, Weber and Kirklin[11] found the duodenum to be the favored site for the benign lesion. Adenocarcinoma was by far the most frequently encountered histopathologic type of malignant tumor of the small intestine in Mayo's series, while most of the rest of the cases were leiomyosarcoma. A greater variety of histopathologic types of benign tumor were seen, but no one type played so dominant a rôle as adenocarcinoma did among the malignant tumors. The high incidence of tumors of the smooth muscle, both benign and malignant, was noteworthy. The distribution of the various histopathologic types of malignant and benign lesions in the several divisions of the small intestine was shown in 2 tables.

A critical study of the cases in the Mayo series[7] revealed that there were 36 cases of the 108 in which the diagnosis should have been made roentgenologically. In 4 of the 36 lesions taken for consideration, the lesion was overlooked completely. In the remaining 32 cases (89%), the presence and site, at least, of a pathologic process was determined roentgenologically. Among these 32 cases there were 8 in which more or less serious misinterpretations detracted from the value of the roentgenologic diagnosis. All of these occurred in cases of carcinoma of the first portion of the duodenum.

An analysis of the cases of tumor of the small intestine encountered at the Mayo Clinic during the years 1930 to 1939, inclusive, revealed 62 cases, 50 of which were of malignant tumor, and 12 of benign tumor. Twenty-six were not pertinent from the viewpoint of roentgenologic diagnosis; in 5 of them no roentgenologic examination of any part of the gastro-intestinal tract was made; in 17 no roentgenologic examination of the small intestine was made, although roentgenologic examination of the stomach or colon or of both was made; in 4 a clinically important lesion was diagnosed correctly in the stomach, colon or duodenum. In 5 of the remaining 36 cases (14%), the lesion of the small intestine was overlooked at the roentgenologic examination. Three of these lesions proved on pathologic examination to be adenocarcinoma; 1, lipoma; 1, submucous hemangioma, 6 mm. in diameter, discovered at pathologic examination of a resected specimen of ileocecal granuloma with persistent postoperative fecal fistula. In the remaining 31 of 36 cases (86%), Weber and Kirklin[11] considered the roentgenologic diagnoses as satisfactory. While a precise pathologic diagnosis was not made in each instance, the lesion was at least recognized and located where the tumor was later found at operation.

Of 62 cases of tumors of the small intestine, 7 occurred in the first portion of the duodenum, 3 in the second portion of the duodenum, and 7 in the third portion of the duodenum. The lesion was identified in 94% and agreed with the diagnosis on microscopic examination in 53% of cases. There were 20 cases in which the tumor occurred in the jejunum. In 1 case no roentgenologic examination of any part of the gastro-intestinal tract was made; in 6, roentgenologic examination of only the stomach or colon or both was made. Of the remaining 13 cases, the lesion was missed in 2 and in 11 a satisfactory roentgenologic diagnosis was offered. In their experience, the ileum seemed to be the most difficult region of the small intestine from the standpoint

of roentgenologic diagnosis. There were 21 cases in which the tumor proved to be in this segment of the small intestine. Four were benign and 17 were malignant tumors. Fifteen of these 21 cases were not considered to be pertinent to their analysis because in 3 of them no roentgenologic examination of any part of the gastro-intestinal tract was made; in 8, roentgenologic examination of only the stomach or colon or both was carried out; and in 4, a clinically important lesion was correctly diagnosed roentgenologically in a part of the gastro-intestinal tract other than the small intestine. The lesion was overlooked in 2 of the remaining 6 cases; in 4 (67%), the lesion was recognized at the roentgenologic examination. The ileum, especially in that part of it adoral to its lowermost 12 inches (30 cm.) they found, offered the greatest difficulty in diagnosis, chiefly because it was difficult to maintain a distended concentration of the contrast suspension there, and because these segments tended to seek such a low level in the pelvis that they were elevated from there often with greatest difficulty.

Considering the roentgenologic manifestations of tumors of the small intestine, Weber and Kirklin[11] stated that the technique of roentgenologic examination cannot be standardized precisely, because occasionally it must be changed in certain respects to suit individual cases. Briefly stated, the upper segments of the small intestine, the duodenum, the jejunum, and the upper two-thirds or so of the ileum were observed roentgenologically by following the progress of a simple mixture of equal parts of barium sulfate and water through these segments. In their experience, the lowermost third of the ileum was usually studied to best advantage by filling it with contrast suspension in retrograde direction through the ileocecal orifice, roentgenoscopic and roentgenographic examinations being made after the bulk of the contrast material had been expelled from the colon. They were of the opinion that the roentgenoscopic examination was the cardinal roentgenologic maneuver, whether the contrast material was administered orally or rectally, and that no number of interval roentgenograms made without reference to a competent roentgenoscopic examination could supplant it satisfactorily.

Like the colon, they stated, the small intestine was a tubular organ. These divisions of the alimentary tract resembled each other in every important morphologic and physiologic respect. The pathologic processes which occurred in them were similar, and both divisions were deformed by such processes in similar ways. Hence, they were convinced, it was possible to apply the same roentgenologic criteria of diagnosis to the small intestine as had been found reliable in the diagnosis of the normal and abnormal large intestine.

Pathologic processes deformed the tubular segment and it was chiefly by the roentgenologic demonstration of such deformities that the presence of disease was determined. One type of pathologic process was distinguished from others by analysis of the morphologic features of the deformity produced and by interpretation of them in terms of pathologic anatomy. The term "deformity" included the concept of that familiar term in roentgenologic literature, the "filling defect," which may be defined as a subtraction from the normal luminal outline, and the concept antithetic to this, namely, an addition to the normal luminal outline, of which the diverticulum and the penetrating ulcer were

most familiar examples. Tumors, both benign and malignant, deformed all segments of the alimentary tract, especially the simple tubular ones, like the esophagus, small intestine and colon, in a way peculiar to themselves. The deformity produced by a tumor might be marginal or encircling, in whole or in part, such as the one produced by an annular carcinoma, or it might be internal or central, such as is produced by the lesions known as polyps or polypoid lesions. In any case, the "filling defect" produced by tumors not complicated by perforation was relatively short and was sharply demarcated aborally and adorally, and the mucosal pattern throughout the extent of the defect was obliterated.

Tumors, in their experience, arising in the submucous structures frequently did not actually invade and destroy the mucous membrane over them, but when they became large enough to be recognized roentgenologically, they obliterated the mucosal pattern over them if in no other way than by stretching the mucous membrane to the point of obliterating its folds, the basis for the mucosal pattern. They found that tumors of the colon and small intestine often produced obstruction of such a degree that the morphologic features of the lesion were not manifested roentgenologically. In such instances it might be impossible to render a more specific roentgenologic diagnosis than that of obstructing lesion. A similar situation developed in cases of intussusception whether it was entero-enteral, enterocolic or colocolic. In adults primary intussusception was so rarely encountered that for practical purposes it could be said that the condition was not seen except with tumor as its cause.

Attention was called to the fact that tumors and other lesions of organs contiguous to or very near the small intestine might extend to it and involve it segmentally, producing a roentgenologic picture similar in many respects to that produced by primary intestinal tumors. Lesions, especially cysts and tumors, of the pancreas were particularly prone to do this. The roentgenologic evidence of the essentially extra-enteral nature of this process was usually demonstrable at the roentgenoscopic examination. Such extrinsic lesions were usually large and thus careful palpation under roentgenoscopic control would almost always yield the key to the correct diagnosis.

These were the cardinal signs from which the roentgenologic examiner derived the concept of tumor, using that term in its narrower sense to signify blastoma, as distinguished from inflammatory tumors or granulomatous processes. These signs, they stressed, must be understood to be but gross morphologic evidences. It was impossible, as a rule, to derive from them reliable concepts regarding the histopathologic nature of the tumor, such as its malignancy or non-malignancy, and the histologic type of tissue of which it was composed.

Their expressed opinion was that the rule may be stated that there are no reliable roentgenologic evidences of benignancy once the evidence for tumor was produced. Certain lesions might manifest all the so-called classical gross morphologic evidences of benign tumors. Such lesions might, on microscopic examination, prove to be true malignant lesions. They felt that this held particularly true for such tumors when they were found in the gastro-intestinal tract. The roentgenologic examiner, then, since he was dealing with gross morphologic characters of lesions, rarely if ever could elicit diagnostic data on which

he could guarantee the benignancy of a tumor he had discovered. He might say that the lesion he had found "looked" like a benign lesion to him. His opinion might later be proved correct in most instances, but his medical and surgical consultants had best not consider his diagnostic guess too seriously, but prefer to consider the morphologic features he described and treat the lesion as a malignant one until competent histologic study proved its true nature.

Lesions that were not tumors deformed the tubular segments of the intestinal tract in a different way. As a group, they tended to extend over longer segments, producing longer deformities. Demarcation between involved and uninvolved segments, in their experience, was gradual, not abrupt. Depending on the pathologic nature and the severity of the disease producing the deformity, the mucous membrane might or might not be destroyed, and the mucosal pattern was correspondingly altered. Even when the mucosal pattern was obliterated completely by ulceration, however, the mucosal relief had a different roentgenologic appearance than that of the relief pattern of tumors. The experienced roentgenologic examiner, they asserted, recognizes a typical mucosal relief pattern associated with tumors, and especially with malignant tumors. He makes use of his familiarity with this pattern in instances in which a malignant tumor has perforated. In this event the lesion takes many of the morphologic characteristics of the inflammatory, tumefactive processes, and it is only by eliciting what may be called the typical mucosal relief pattern of malignant tumor that the roentgenologic examiner can arrive at a diagnosis of the true nature of such lesions.

These authors felt that roentgenologic examination had a very real contribution to make to the diagnosis of lesions of the small intestine. They acknowledged that roentgenologic examination of this division of the alimentary tract had not approached the efficiency of the roentgenologic method applied to the divisions above and below it. Such efficiency, they thought, perhaps was too much to hope for. They were of the opinion that with accumulating experience improvement would come and, with greater interest in this examination on the part of their clinical and surgical consultants and greater reliance on it, that more lesions would be discovered. It was their hope that accumulating clinical experience would eventually lead to a better selection of cases for roentgenologic examination and that through this many a patient would gain the advantage of earlier treatment than at present for these otherwise, for the most part, hopeless conditions.

That carcinoma of the duodenum was a rare condition and therefore of unusual interest to the clinician and the roentgenologist, was the conclusion of Ritvo and Hewes[10] after the study of the records of all patients admitted to the Pondville Hospital. This institution, under the auspices of the Massachusetts Department of Public Health, is limited to the diagnosis and treatment of growths of a malignant nature and has been functioning for 12 years. Among 16,000 patients admitted and on whom 1655 autopsies were made, only 3 proved cases of carcinoma of the duodenum were found. This incidence rate of 0.02% was in agreement with those reported from the study of other series; these varied from 0.03 to 0.06%.

They found carcinoma of the duodenum to be essentially a disease

of the later decades of life. In their series, the youngest patient was 63 years of age and the oldest 80 years, the average being 70 years. In the cases which they found in reviewing the literature, the ages varied from 37 to 80 years (general average, 48.3 years). This was in striking contrast to carcinoma of the stomach and colon, in which the lesions occurred in patients as young as 13 years of age. Males were affected in the ratio of about 2 to 1.

No constant predisposing factor for carcinoma of the duodenum was determined. There was no apparent relation to peptic ulcer or any other lesion in the gastro-intestinal tract. Nor were there any demonstrable nutritional, occupational, or hereditary factors. None of the patients in their series presented long-standing stomach or bowel complaints. Symptoms were usually of a few months' duration; on only 1 instance did the history extend over a period as long as 2 years.

Their study revealed that carcinoma may occur in any portion of the duodenum. The second portion was frequently involved (62%) and the first portion was the next most frequently involved (25%). Neoplasms were found in the third portion in 13% of cases. Adenocarcinoma arising from the mucosa constituted 90% of the cases. Scirrhous or colloid growths were the rule. Sarcomatous lesions were found in only 2 to 5% of instances. The gross findings were most frequently those of an annular, constricting neoplasm which in some instances completely encircled the lumen. This type was particularly prone to occur in the first and second portions. In the third portion of the duodenum, the growth was more apt to be large and fungating. The sarcomas were usually softer and non-constricting. Stenosis, they found, occurred relatively early and frequently in the lesions involving the duodenal cap. In the neoplasms occurring in the third portion, obstruction was a late and common development. Involvement of the ampulla of Vater was not common. Practically all of the lesions involving the second portion of the duodenum, however, eventually caused obstruction of the bile ducts with resultant jaundice. It was at times impossible to state with certainty whether the growth originated in the duodenum or in the ampulla itself. One case was reported as having occurred primarily in a diverticulum. This was explained by the fact that the mucosa lining the diverticulum was usually the same as that in the duodenum itself.

The clinical symptomatology of carcinoma of the duodenum they found to be indefinite, variable, and usually not pathognomonic. As a rule, the onset was gradual and insidious. Pain might only be slight or it might be absent. When present, it was located in the epigastrium or right upper quadrant, and was usually dull in character, although rarely it might be sharp and colicky. Weight loss was marked and rapid. Vomiting was a feature when the lesion caused stenosis and blood and bile, along with undigested food particles, were frequently present. Anemia was usually severe. Jaundice occurred in about 20% of cases and rarely might be intermittent in character. Biliary colic might be present in the later stages of the disease.

The symptoms were, as a rule, of short duration, the length of time during which complaints were present averaged about 4 months. If the duodenum became completely blocked, the usual manifestations of

obstruction were predominant. Involvement of the ampulla of Vater produced the typical changes associated with jaundice.

In their experience, the physical findings were usually negative in the early stages. As growth progressed, the anemia and wasting characteristic of advancing carcinoma became more evident. A mass in the mid-epigastric region was palpable in about 50% of cases. Frequently there was enlargement of the liver and the gall bladder was palpably enlarged.

Laboratory findings were variable in their cases and often were of little or no aid in arriving at the diagnosis. Increased hydrochloric acid in the gastric contents was present, as a rule. Blood and bile were frequently found in the vomitus and the finding of blood with absence of bile on duodenal drainage was of special significance and indicated to them the possibility of a neoplasm involving the duodenum. Changed blood in the stools or tarry stools occurred, but this finding was not particularly helpful because it was common to so many conditions.

The roentgenologic findings in their cases were in agreement with those already presented.

The differential diagnosis of carcinoma of the duodenum, they asserted, presented especial difficulties because strikingly similar features characterized many other conditions. Carcinoma of the bile ducts or ampulla of Vater with invasion of the duodenum, for example, might be impossible to distinguish from duodenal carcinoma. Carcinoma of the head and body of the pancreas presented roentgenologic characters by which it could be differentiated and obstruction did not result, as a rule, from lesions involving the pancreas.

Lymphoblastoma and lymphosarcoma exhibited definite patterns in roentgenologic examination with simultaneous lesions of the lymphoid structures in various parts of the body and enlargement of the spleen. The rate of growth, as demonstrated by periodic reëxamination, was much more rapid than it was in carcinoma. The response to adequate Roentgen therapy was prompt and striking in the lymphoid type of lesions, and this was often of great value in the making of the diagnosis.

Carcinoma involving the stomach, particularly in the region of the pylorus, could usually be differentiated by roentgenologic examination and was also characterized by the absence of free hydrochloric acid in the stomach.

In acute or chronic pancreatitis, there was no change in the acidity of the gastric contents, blood in the vomitus or stools was absent, and the pain which was the outstanding feature of pancreatitis was acute and severe.

Impaction of a gall stone in the duodenum, while of rare occurrence, might be difficult to differentiate from carcinoma of the duodenum. If the stone did not cause complete obstruction, the smooth, round borders would suggest a polyp rather than a malignant neoplasm. With complete blocking of the lumen of the intestine by a calculus, the sharp, rounded superior margins of the stone felt on palpation should suggest the proper diagnosis. Roentgenographic examination of the abdomen prior to administration of a contrast medium might reveal the calculus under favorable circumstances.

Adhesions about the duodenum, either postoperative or as a sequel to pericholecystitis, diverticulum of the duodenum, and deformity

following extensive scarring from the healing of duodenal ulcers might in their symptomatology closely simulate carcinoma of the duodenum. Roentgenologic examination and reëxamination were most helpful in the making of the differential diagnosis and some clinical features were stated that had been found of value.

Duodenal obstruction, they pointed out, might also result from external pressure. Among the chief causes of this they listed: enlargement of the gall bladder, tumors of the omentum, pancreas or liver; enlarged retroperitoneal nodes and other tumefactions in this region; aneurysms of the celiac axis at the hepatic artery; and pressure from the superior mesenteric vessels. If the stenosis was partial or intermittent, differentiation might be possible. With complete obstruction, however, the cause of the stenosis could only rarely be determined.

In the treatment of carcinoma of the duodenum, Ritvo and Hewes[10] found medical therapeutic measures of value as a supportive measure. In the presence of dehydration the administration of fluids orally or by injection methods was indicated. Anemia and lack of adequate vitamin content had to be prevented when possible and sufficiently treated when they presented. Transfusions were administered when necessary. Explorative laparotomy was indicated if the roentgenologic evidence pointed strongly to duodenal neoplasm, as the only hope of relief rested on prompt operative intervention. Surgical relief might be impossible even in the first stages of the disease because of the location of the primary growth, but if intervention was delayed until the diagnosis was established with certainty, it would doubtless be too late to effect a cure. Palliative surgery, such as resection or short-circuiting for the relief of obstruction, should be resorted to whenever necessary as it might serve to diminish suffering and possibly to save life.

Roentgen and radium therapy, in their experience, offered little of real value because of the location of the growth. These measures did, however, offer something as palliative procedures and in the differential diagnosis of lymphosarcomas which, as before mentioned, responded promptly and remarkably to radiotherapy.

The prognosis in carcinoma of the duodenum, they averred, was poor. The average duration of life was 6 to 8 months. The longest period of survival, in their knowledge, was about 2 years. Surgical intervention, while of importance for palliation, did not in the cases reported appear to have any great value in the prolongation of the life of any of these patients.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of "milligrams per cent"—is well covered on Page 53 of the American Medical Association's book entitled "Medical Writing": "Results of chemical determinations are frequently expressed as 'milligrams per cent' or 'grams per cent.' This means literally 'milligrams (or grams) per hundred milligrams (or grams),' which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as 'milligrams per hundred cubic centimeters' or 'milligrams per 100 gm.' If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply 'per hundred cubic centimeters' the first time the phrase appears and to use merely 'milligrams' (not 'milligrams per cent') thereafter." We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word "consider" as indicating that the item is still under consideration or being meditated upon, *i.e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as "think to be," or "regard as" or "believe to be" or "hold as an opinion" gives the more exact meaning.

THE EDITOR.